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IDIOPATHIC FAMILIAL LIPEMIA[1,2]

L. EMMETT HOLT, JR., FRANCIS X. AYLWARD[3] AND HARRY G. TIMBRES[4]

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Submitted for publication March 31, 1939

The subject of lipemia has been discussed by various reviewers (1–7). Most commonly it is found with *diabetes mellitus* or *nephrosis*. It may occur in *liver disease* when conditions are such that fat digestion is not impaired but the internal utilization of fat is interfered with. When obstructive jaundice is present lipemia may be masked; as much as 3 per cent or 4 per cent of fat may be found in the serum (6) without any change in its gross appearance—a state of affairs attributed to finer emulsification of fat due to the presence of bile salts. In other forms of liver disease with lipemia, the typical lactescence of the serum may be found. Various *poisons* may give rise to lipemia; in many of these—such as phosphorus, chloroform, carbon tetrachloride, phloridzin and chronic alcoholism—it seems likely that the effect can be attributed to liver damage. In other cases: ether narcosis, carbon monoxide poisoning, it may be that anoxemia plays a part; in still others the explanation is obscure. Achard and his collaborators (8) in attempting to produce amyloidosis in animals by injections of sodium caseinate made the interesting observation that certain individual animals failed to develop amyloid but developed lipemia instead. The recent observation of lipemia in Von Gierke's disease (9) may well be due to impaired hepatic function.

Quite apart from diabetes, *pancreatic disease* may produce lipemia;

[1] The study was aided by a Grant from Mead Johnson and Company, Evansville, Indiana for the study of fat metabolism.

[2] A preliminary report of this patient was presented at the 28th Annual Meeting of the American Society for Clinical Investigation in Atlantic City, May 4, 1936, an abstract of which was published in *J. Clin. Invest.* **15**: 451, 1936.

[3] Commonwealth Fund Fellow.

[4] Deceased.

this has been recognized clinically (10) and has been produced experimentally (11). In *pregnancy* a moderate degree of lipemia is often found (12). In *hypothyroidism* (13) and in some cases of *cerebral obesity* (14) with low basal metabolic rate lipemia may occur. The difficulty here seems to be analogous to the *alimentary lipemia* which can be obtained in the normal individual after the ingestion of a sufficiently large quantity of fat—there is a plethora of fat in relation to the metabolic requirements. In certain animals having a marked ability to transform carbohydrate into fat, such as the goose, stuffing with carbohydrate produces a persistent alimentary lipemia; this, however, has not been observed in man. Lipemia occurs in various *anemic states*; at times it has been observed in chronic anemias and leukemia, but more particularly it is found with acute anemias—post-hemorrhagic anemia (15), purpura fulminans (16); the lipemia described in the post-operative state (17) may well be due to loss of blood. In certain animals *anoxemia* and *cachectic states* produced by starvation, inadequate diets or other means will cause lipemia and there are instances in man attributable to these causes. The usual explanation for the anemic, anoxemic or cachectic group has been that partially starved tissues—due to lack of food or oxygen—send out a call for food to which the depots respond by excessive fat mobilization. It is possible, however, that the difficulty here is with the liver; Rich, Bumstead and Barron (18) have shown how susceptible the liver is to anoxemia and to anemia. The so-called *lipoidoses*—Gaucher's disease, Niemann-Pick disease and generalized xanthomatosis—are usually attributed to storage of abnormal lipids, which circulate in the blood, but there is inadequate evidence for this conclusion. Blood studies of the first two are practically non-existent; in the case of xanthomatosis the finding of increased cholesterol esters in the blood is an inconstant one. Recently there has been mention in the literature of a relation between excessive blood lipids and certain dermatoses, notably psoriasis (19). Here again, however, the evidence is conflicting.

Aside from the pathological conditions mentioned above there are cases of lipemia (20) which do not fit into any of these categories, which for want of a better term may be labelled idiopathic. Because of the rarity of this condition and of certain unusual features which

we have had an opportunity to observe, the present case report has seemed justified.

CASE REPORT

C. B. (H.L.H. No. 94267), an eleven year old girl, was brought to the Harriet Lane Home on September 16, 1935 with the complaint of chronic ulcers of the leg and periodic abdominal attacks.

The family history was non-contributory. The father (38 years old) and mother (34 years old) were in good health. Two older children and a younger child were likewise healthy. Three siblings had died in infancy—one from meningitis, one from pneumonia and one from summer diarrhea. There was no history of chronic disease in the family.

The patient had been regarded as normal up to the age of four years. She was born at term without complications of labor or postnatal disturbances. She had been breast fed for eleven months and then fed artificially without difficulty. The diet had at times been seriously curtailed by the family pocketbook, but at other times it had been adequate. There was no history of predilection for or aversion to any type of foodstuff. Development and habits were normal. She had had measles, scarlet fever and whooping cough—mild attacks with uneventful recoveries in each instance. She had been successfully vaccinated against smallpox.

The present illness began in the summer of 1928 at the age of four years. A vesicle was noted on the shin of the left leg which soon ruptured leaving a shallow ulcer; this persisted for several months despite local therapy, healing only with the advent of cool weather. Since then similar ulcers have appeared running almost an identical course. They start as a rule from minor injuries, beginning as vesicles which soon ulcerate; they commence in the summer and defy all treatment until the cooler autumn weather comes when they heal promptly; they have always been confined to the left leg.

In addition to the ulcers a generalized skin eruption has been noted involving the scalp, trunk and extremities with red, scaly, discrete lesions. This, too, has appeared in the summer and practically disappeared in the fall.

The abdominal attacks began a few months after the onset of the skin lesions. On December 12, 1928, the patient was seized with a sudden pain in the abdomen, followed by projectile vomiting, fever, abdominal rigidity and collapse. She was taken to a hospital at Morgantown, West Virginia, where a laparotomy was performed at once. A small amount of yellow fluid was found in the peritoneal cavity which was negative on culture; the duodenum was said to be slate-gray in color but no other abnormality was noted. The abdomen was drained and the patient made an uneventful recovery. Acetonuria was noted during convalescence. In retrospect a diagnosis of probable acute pancreatitis was made. The pancreas itself was not examined by the surgeon.

A second attack, similar in nature, occurred on March 28, 1929. The patient

was again admitted to the hospital, but was not operated upon. A blood count showed white blood cells 14,600. She began to improve shortly after entering the hospital and was discharged cured within a few days. Since then there have been several similar attacks with intervals of months between them. These were diagnosed appendicitis, gastritis, enteritis, *etc.*, by various physicians, but no further exploration was attempted. The last attack occurred two years before admission to the Harriet Lane Home.

Aside from the skin lesions and the abdominal attacks the child seemed fairly well but was regarded as somewhat sickly by her parents. She was seen by one of us (H. G. T.) in July, 1935, who met with no success in treating the skin ulcers. Blood was taken for a Wassermann test and the serum which separated had the appearance of thick cream. On this account she was sent to Baltimore for further study.

Admission physical examination showed a child of normal behavior, somewhat undernourished in appearance. Measurements (height 50½ inches; weight 52½ pounds) showed that she was at the lower limit of normal height for her age and was approximately 15 per cent below weight for her height. There were no evidences of puberty. The skin was somewhat dry. There was a right rectus scar with some keloid formation. On the extensor surfaces of the arms, over the shoulders and upper portion of the back numerous circular depigmented areas were noted, some as large as 3 cm. in diameter. Over the knees and elbows were reddish, scaly lesions, sometimes confluent, quite typical of psoriasis. A few of these lesions were present on the face and abdomen. On the left leg were three ulcerated areas—one, small and superficial (the most recent one to develop) located in the midportion of the calf, and two larger deep ones, each several centimeters in diameter, one over the internal malleolus and another over the midportion of the tibia. The ulcers were rounded with regular, elevated margins and an indurated base showing abundant granulations and partly covered with greenish purulent material. They were painful to the touch. The underlying bone did not seem to be involved. Close to one of the larger two ulcers was a small pustule from which staphylococcus albus and a hemolytic streptococcus were cultured. In addition to the skin lesions and malnutrition, the physical examination disclosed the presence of several carious molar teeth, and of scarred imbedded tonsils on both sides with small shotty lymph nodes in both posterior cervical triangles. There was an inconstant systolic murmur heard inside the apex of the heart, not transmitted. On deep inspiration the liver and spleen could be palpated as firm masses, the former two finger-breadths and the latter one finger-breadth below the costal margin; there was no abdominal tenderness. The extremities showed no evidence of impaired circulation; their color was good and the dorsalis pedis pulses were both easily palpable.

Routine laboratory studies revealed nothing very illuminating. Urine examinations were consistently normal. The stools were negative for ova and parasites. On admission the blood showed a mild secondary anemia, but twelve days later after a generous diet the red blood cells were 5.29 million per cmm.

and the hemoglobin was 94 per cent. The systolic heart murmur, too, had disappeared. White blood cells ranged between 6,500 and 10,500 per cmm. The polymorphonuclear neutrophiles ranged between 61 per cent and 65 per cent and the eosinophiles between 2 per cent and 5 per cent. Abnormalities in the smear were not noted. A specimen of blood drawn by venepuncture showed the typical milky appearance of the serum previously noted; the total lipids were found by analysis to be 3.1 per cent. Other blood chemical determinations gave essentially normal figures. The fasting blood sugar ranged between 80 and 99 mg. per 100 cc. Glucose tolerance tests (1.25 gm./kg.) gave the following figures:

	TEST NO. 1	TEST NO. 2
	mg. per 100 cc.	*mg. per 100 cc.*
Fasting blood sugar	85	92
½ hour	112	132
1 hour	91	183
2 hours	88	126
3 hours	86	93

Non-protein nitrogen of the whole blood was 43 mg. per 100 cc.; CO_2 combining power 58.2 vol. per cent; serum protein 6.64 per cent; A/G ratio 1.3. Serum sodium 132 to 137 m.eq./L; serum chloride 104 to 104.2 m.eq./L.

The patient thus presented a somewhat bizarre clinical picture. To relate the skin lesions, the lipemia and the enlarged liver and spleen was a somewhat baffling problem. It was not possible to establish the presence of any of the familiar causes of enlargement of the liver and spleen. The skin lesions, except for the asymmetrical distribution and seasonal incidence of the ulcers were in no way remarkable. The psoriasis lesions and scars were typical enough but the ulcers gave no indication of anything other than a pyogenic infection. The patient's tuberculin reaction was negative to 1.0 mg., Dick and Schick tests were negative, as were Wassermann and flocculation tests of the patient's and of the father's blood. Reports of Kahn tests done on both parents by the West Virginia State Board of Health were likewise negative. Cultures from the ulcers made on Sabouraud's medium failed to show any parasitic growth.

The most promising approach seemed to be to investigate the patient for possible causes of lipemia. Diabetes and nephrosis could be excluded at once. We attempted to demonstrate impairment of liver function but met with no success. There was no jaundice, the van

den Bergh reaction was negative and a bilirubin excretion test[5] failed to show any delay in the excretion of intravenously injected bilirubin. The urine gave a negative qualitative test for urobilin. Glucose tolerance curves were essentially normal, as was a levulose tolerance test (1 gram of levulose being given per kg. body weight):

	mg. per 100 cc.
Fasting blood sugar	80
½ hour after levulose	68
1 hour after levulose	105
2 hours after levulose	93
3 hours after levulose	86

On a subsequent occasion a blood esterase test failed to show the characteristic increase found in liver disease. It was not possible to obtain a history of ingestion of any poison or indeed of any abnormal substance in the diet or environment.

Efforts to demonstrate a pancreatic lesion were equally disappointing. Fluoroscopy of the duodenum after a barium meal showed no abnormality of any kind. The stools contained no excess of fat, and the urinary diastase—a test which has been much stressed in the German literature—failed to show the abnormally high figures reported in cases of pancreatic disease. Studies of the blood, too, were essentially negative. The mild secondary anemia which had been present on admission cleared up rapidly. A fragility test gave normal figures, hemolysis commencing in the 0.42 per cent solution and being complete in the 0.32 per cent solution. A preparation set up for sickling was likewise negative. The sedimentation rate was, however, somewhat accelerated (23 mm. in 1 hour, Cutler method); this test was unfortunately not repeated. There was no evidence of any familiar endocrine disorder. Because of the dryness of the skin a basal metabolism test was done which gave a figure of −12 per cent. X-rays of the chest, sinuses, head and the long bones were negative. There was no evidence of deficiency disease; the diet for the past year as far as it could be ascertained did not seem to be deficient. It was not possible to regard the condition as an alimentary lipemia for no unusual quantity of fat had been ingested; if anything the intake of fat had been below the average. We were, therefore, forced to the

[5] Performed for us by the Chemical Laboratory of the Department of Medicine.

conclusion that the patient belonged in that unsatisfactory group of idiopathic lipemias.

Further studies were commenced in the hope of throwing light upon the nature of the metabolic anomaly, but they were interrupted by an unexpected complication. A second blood sample taken ten days after admission showed a higher total lipid concentration (7.37 per

FIG. 1. *Fundus of patient, C. B., showing typical appearance of lipemia retinalis.* The characteristic feature is the appearance of the vessels which are pink-cream in color on emerging from the nerve head, becoming pure cream at the periphery of the fundus. The color makes it impossible to distinguish arteries from veins. As far as we are aware, this patient and her brother are the only non-diabetic subjects in whom lipemia retinalis has been reported. (Reproduced by courtesy of Dr. Alan C. Woods.)

cent) than was found on admission. At about the same time examination of the eye-grounds, which had previously been reported as normal, showed in a very striking way the appearance of lipemia retinalis. In the vicinity of the disc the vessels were pink-cream in color, but as they approached the periphery of the fundus they took on a pure cream color. One week after this the patient awoke early in the morning complaining of abdominal pain. The pain increased

rapidly in severity; it was colicky and localized chiefly in the epigastrium although it radiated over the entire abdomen. Morphia was required for its relief. The onset of the pain was marked by nausea and vomiting, the vomitus soon becoming bile-stained. Four hours after the onset of the attack she presented a distressing picture of collapse. She was pale and cyanotic. Although morphine had relieved the pain in large part she complained of a subjective feeling of suffocation. The pulse was rapid (140 to 150 per minute) and so weak that it was scarcely palpable; the blood pressure was unreadable (later, after a glucose infusion, a reading of 66/20 was obtained). The tongue was coated. The abdomen showed exquisite tenderness and a board-like rigidity which prevented satisfactory palpation. The tenderness seemed increased over the liver and spleen in particular. There was no abdominal distention, and a normal stool was passed at this time. The abdominal and thoracic veins were, however, greatly engorged with a current flowing upwards. The temperature had risen to 38.4°C. The white count was 27,300; polymorphonuclears 86 per cent. Urine showed no acetonuria. CO_2 capacity was 48 vols. per cent. The following day the patient was somewhat improved. On the third day the improvement was striking and pain had virtually disappeared. On the fourth day she had completely recovered.

As the abdominal pain and rigidity subsided and the abdomen could again be palpated it was noted that a very striking increase had taken place in the size of the liver and spleen. The liver, which before could be felt only after deep inspiration, now presented an edge 3 or 4 finger-breadths below the costal margin; the spleen, too, was far more readily palpable, extending 3 finger-breadths below the costal margin with deep inspiration. During the succeeding week or two this enlargement became less striking and two weeks after the attack the outlines of these organs were essentially the same as on admission. The engorgement of the abdominal veins, too, decreased gradually following the attack and two weeks later there was nothing striking about their appearance. Most astonishing, however, was the change in the appearance of the fundus oculi. Twenty-eight hours after the onset of the attack there was not a trace of lipemia retinalis noticeable. A determination of the blood lipids made on the fifth day

after the onset of the attack showed that they had fallen to 2.07 per cent, and that the serum had lost its milky appearance almost completely. The improvement in the lipemia following the attack proved, however, to be very temporary. One week after the close of the attack the blood lipids had risen to 3.46 per cent and four days after that to 6.1 per cent. At the latter time, the lipemia retinalis was found to have returned.

During the period in which the patient remained under observation in the hospital, five of these attacks were observed—all of them essentially similar to the one described. Their duration was from two to four days; the shorter attacks seemed to be accompanied by a higher fever (40°C. on one occasion) than the longer attacks. The symptoms of pain and collapse were of similar character in both types of attack. With each attack engorgement of the abdominal veins was noted, and following each attack the liver and spleen were found to have increased in size, whereas the lipemia and the lipemic appearance of the retina had disappeared. Carefully timed chemical observations showed that the critical level for blood fat was in the neighborhood of 8 per cent. When the blood fat exceeded this figure an attack ensued within a few hours. The reduction in the blood fat was found to be very rapid and to occur chiefly on the first day of the attack, particularly during the first few hours of severe pain, when it would be reduced by approximately 1 per cent an hour; the lowest levels (1.3 per cent to 1.5 per cent) were usually attained on the second day of the attack; these seldom persisted more than a day or two. Lactescence of the serum was noticeable except when the fat was less than 2 per cent; when it was between 2.5 per cent and 3 per cent, lipemia of the retina became noticeable. The latter first made its appearance and was always more striking in the peripheral retinal vessels.

Although the patient took no food during the attack the rapid fall in the blood fat could not be attributed to starvation. A later experiment in which the patient was fasted between attacks, showed no striking diminution of blood fat. Since there was no evidence of abnormal excretion of fat—either in the urine or stools—during an attack, it was our conclusion that the fat removed from the blood went to the liver and spleen, and that its accumulation there gave rise to

the enlargement of these organs, the acute distention of their capsules causing the pain, and that some interference with the portal circulation, due to the accumulation of fat, gave rise to the engorgement of the abdominal veins. Laparotomy was not deemed justifiable and this hypothesis could, therefore, not be verified.

In the intervals between attacks various studies were carried out with a view to obtaining some understanding of the condition and possibly some clue for rational therapy. Repeated determinations of the lipid partition in the blood are found in table 1. They showed that the lipemia was due almost entirely to an increase in neutral fat. As the lipemia increased after attacks there was some rise in the lipid phosphorus and in the total cholesterol, but even at the maximum these two were scarcely double the normal values whereas the neutral fat at such times was fully fifteen times the normal value. A determination of the free and combined cholesterol[6] was very kindly made for us by Dr. Warren M. Sperry. This gave the following results:

	mg. per 100 cc.
Total cholesterol	330.3
Free cholesterol	127.5
Ester cholesterol	202.8

$$\text{Ratio } \frac{\text{Ester cholesterol}}{\text{Free cholesterol}} = 1.59 \text{ (normal} = 2.3\text{–}3.2\text{)}$$

The low ratio (the so-called "estersturz" of German writers) has been noted only in the presence of liver disease and of infections.

The esterification of the serum *in vitro* was also tested for us by Dr. Sperry. On incubating for four days a gradual decrease in free cholesterol and increase in ester cholesterol occurred, the ratio reaching 3.02 in four days. This degree of esterification *in vitro* is regarded by Dr. Sperry as within the normal limits. Why normal esterification occurs *in vitro* when it is definitely impaired *in vivo* is not clear.

The iodine value of the total lipids was found to be 61.6 at the height of the lipemia and 68.9 after an attack; thus it would appear that the excess fat had the characteristics of depot fat. We attempted to ascertain if the fat were tied up in some unusual combination in the blood which might interfere with its normal utilization. The amount

[6] On May 12, 1936.

TABLE 1

Course of serum lipids in patient C. B.

DATE	TOTAL LIPIDS (NORMAL VALUE* 0.57–0.82)	TOTAL CHOLESTEROL (NORMAL VALUE* 100–230)	LIPID PHOSPHORUS (NORMAL VALUE* 7–14)	REMARKS
1935	*gm. per 100 cc. serum*	*mg. per 100 cc. serum*	*mg. per 100 cc. serum*	
Sept. 18	3.10	300	19.4	Patient on regular ward diet
Sept. 27	7.37	210	17.2	
Oct. 6				Abdominal attack no. 1
Oct. 11	2.07	192	15.6	
Oct. 18	3.46	212	12.9	
Oct. 22	6.10	201	15.6	
Oct. 26 (10 a.m.)	4.28	215	7.5	Abdominal attack no. 2. Specimen taken 5 hrs. after onset
Oct. 26 (4 p.m.)	2.63	199	7.6	
Oct. 26 (10 p.m)	1.45	203	9.2	
Oct. 27	1.91	205	10.0	
Oct. 28	1.35	182	6.2	
Oct. 29	1.37	197	11.4	Lecithin 7 gm./day started
Nov. 1	3.34	246	13.1	
Nov. 2	1.94	225	11.3	
Nov. 6	2.69	230	11.8	
Nov. 11	4.18	214	15.1	
Nov. 15	3.06	197	12.2	
Nov. 18	3.72	199	12.5	
Nov. 21	4.35	235	13.9	Choline 5 gm./d. started. Lecithin stopped
Nov. 25	4.36	241	14.2	
Dec. 1				Weighed diet begun: P. 70, F. 50, C. 150. Choline stopped
Dec. 3	5.85	263	15.3	
Dec. 6	6.49	289	16.7	
Dec. 7	6.86	274	16.6	
Dec. 10	7.53	301	18.1	
Dec. 10–12				48 hrs. starvation
Dec. 12	6.00	294	17.2	
Dec. 16 (a.m.)	8.10	331	18.5	Abdominal attack no. 3. Specimen taken 1 hr. before
Dec. 16 (8 p.m.)	4.75	257	16.2	9 hrs. after onset of attack
Dec. 17	3.44	260	14.0	
Dec. 17 (8 p.m.)	3.68	275	13.3	
Dec. 18	2.08	197	10.1	
Dec. 20	3.44	232	11.6	
Dec. 24	4.48	310	13.9	Transfused from L. K.
Dec. 26	1.57	153	8.2	
Dec. 30	5.03	228	15.6	

TABLE 1—*Continued*

DATE	TOTAL LIPIDS (NORMAL VALUE* 0.57–0.82)	TOTAL CHOLESTEROL (NORMAL VALUE* 100–230)	LIPID PHOSPHORUS (NORMAL VALUE* 7–14)	REMARKS
1936	*gm. per 100 cc. serum*	*mg. per 100 cc. serum*	*mg. per 100 cc. serum*	
Jan. 2	2.30	191	12.6	
Jan. 3	2.53	197	10.5	
Jan. 7	4.27	197	15.6	
Jan. 13	7.12	273	18.5	Transfused from R. W.
Jan. 15	6.18	254	17.5	Abdominal attack no. 4. Specimen taken 1 hr.(?) after onset of attack
Jan. 15 (2 p.m.)	3.34	252	9.33	
Jan. 16	1.47	200	6.00	
Jan. 17	1.92	205	8.67	
Jan. 21	4.78	253	10.3	
Jan. 23	5.62	260	13.6	Thyroxin given
Jan. 24	6.13	291	15.7	
Jan. 25	5.73	289	12.7	
Jan. 27	6.77	327	13.2	Insulin started
Jan. 29	7.33	321	16.7	
Jan. 30				Insulin discontinued
Feb. 1	8.04	339	18.6	Abdominal attack no. 5. Specimen obtained before onset
Feb. 3	1.42	194	10.8	
Feb. 6	2.94	195	14.2	Liver extract started
Feb. 9				Liver extract discontinued
Feb. 10	4.61	231	14.7	
Feb. 11	4.76	232	15.1	Transfused from L. K.
Feb. 12	3.78	226	13.7	
Feb. 13	3.76	235	14.2	
Feb. 17	6.10	295	18.1	Anterior pituitary started
Feb. 19	8.20	398	18.1	Anterior pituitary stopped
Feb. 19–21				2 day fast. No attack
Feb. 21	4.81	305	17.5	Transfused from L. K.
Feb. 22	5.65	301	18.6	
Feb. 23	5.02	280	16.0	Low fat diet (not over 15 gm./d.) + 5 gm. choline
Feb. 24	5.71	260	15.8	
Feb. 28	4.10	241	15.5	
Mar. 3	2.60	232	9.6	
Mar. 9	1.88	201	9.3	
Mar. 12	2.46	209	10.1	
Mar. 19	2.45	221	10.7	
Mar. 23	3.92	225	10.9	
Mar. 26	3.15	233	10.1	
Mar. 31	3.42	251	11.3	

TABLE 1—*Concluded*

DATE	TOTAL LIPIDS (NORMAL VALUE* 0.57–0.82)	TOTAL CHOLESTEROL (NORMAL VALUE* 100–230)	LIPID PHOSPHORUS (NORMAL VALUE* 7–14)	REMARKS
1936	*gm. per 100 cc. serum*	*mg. per 100 cc. serum*	*mg. per 100 cc. serum*	
Apr. 4	4.06	262	11.9	
Apr. 8	2.90	250	10.9	
Apr. 9				Choline stopped
Apr. 10	2.19	231	10.7	
Apr. 13	4.81	274	12.1	
Apr. 16	4.97	282	12.4	
Apr. 20	3.68	291	11.6	
Apr. 23	4.16	265	11.7	
Apr. 26	4.37	272	12.0	
Apr. 29	4.49	269	12.1	
May 2	3.87	250	11.4	
May 7	3.99	241	11.1	
May 11	3.68	254	12.0	
May 12				Choline 9 gm./day started
May 13	3.12	251	10.7	
May 17	3.26	231	11.3	
May 20	3.94	247	11.9	
May 23	4.48	239	11.8	
May 26	3.15	235	11.1	
May 27				Choline stopped
May 28				Fat reduced to 8 gm./day
May 29	3.61	230	12.7	
June 1	3.08	247	12.3	
June 5	2.27	229	11.5	
June 9	2.33	238	11.6	
June 23				Sent home on diet not to exceed 10 gm. fat per day
Sept. 9	3.80	241	12.9	
Nov. 13	2.59	221	10.7	
1937				
May 15	2.71	219	11.0	Lipocaic started
June 7	3.26			Lipocaic stopped
1938				
July 14	2.20	146	12.1	
Oct. 24	1.70			

* From Peters and Van Slyke: *Quantitative Clinical Chemistry.* I. *Interpretations.* p. 238. (Williams & Wilkins, Baltimore, 1931.)

of lipid combined with protein was estimated by comparing the total lipid extracted with alcohol and ether (3:1), with that obtained by

extracting with ether alone (which presumably represented the fraction uncombined with protein). It was found that when the total lipids were 7.33 per cent, 6.55 per cent could be extracted by ether alone, and on an occasion when the total lipids were 3.44 per cent, 2.76 per cent could be extracted by ether alone. Although the absolute values for lipid combined with protein (0.78 per cent and 0.68 per cent) are somewhat greater than those reported in normal subjects by Macheboeuf and Wahl (21) (0.4 per cent), it is quite apparent that combinations with protein will account for only a negligible part of the increase in blood fat. Because of the suggestion of Peters and Man (22) that a certain amount of lipid might be combined with chlorine, estimations of lipoid chlorine were made; only infinitesimal traces of chlorine were found in the lipid extract, following Peters' procedure. Failing to demonstrate the presence of unusual lipid combinations we turned our attention to a study of the fat burning mechanism. The respiratory quotient, studied on two occasions after an overnight fast, gave values of 0.749 and 0.767 respectively. The administration of carbohydrate on the first occasion (1.25 grams glucose per kilogram, by mouth) caused the quotient to rise to 0.867 after one hour; after two hours it was 0.833. On the occasion of the second test 3 ounces of olive oil were taken by mouth and the following quotients were observed:

	Respiratory quotient
Fasting	0.767
1 hour after oil	0.784
3 hours after oil	0.788
5 hours after oil	0.770
6½ hours after oil	0.744

These fasting quotients and responses to the administration of carbohydrate and fat we regarded as normal. The fall in quotient obtained 6½ hours after fat administration, though slight, we believe is significant of an increased combustion of fat. A fall in quotient due to increased oxidation of fat following fat administration is always difficult to demonstrate. Murlin and Lusk (23) and others who have worked in this field found that it could be produced only after the ingestion of large quantities of fat, that the drop was never very marked and that as a rule it reached its maximum extent between

the sixth and tenth hour. These tests were made in an interval between attacks, at a time when the blood fat was high and was rising. The normal quotients obtained at this time speak against the possibility of a pathological degree of fat formation from carbohydrate. If a defect in fat burning were present it would hardly have been possible to demonstrate the late fall in R.Q. after fat administration. Further evidence of ability to burn fat was the prompt appearance of ketone bodies in the urine on fasting. The patient was given a sixty hour fast; within twenty-four hours marked ketonuria had developed, qualitative tests reaching maximum values thirty-six hours after the onset of the fast.

An attempt was made to study the respiratory metabolism during an attack, but owing to poor coöperation this was unsuccessful. Through the courtesy of Dr. C. N. H. Long[7] estimations were made of the ketogenic hormone (Anselmino and Hoffmann (24)) in the urine of our patient. The results were somewhat inconsistent. A specimen obtained during an attack showed a ketogenic response of 4.5 mg./100 gm. rat/day (normal up to 4.14 mg.) whereas a control specimen between attacks showed 3.8 mg./100 gm. rat/day. A specimen obtained just before an attack gave inconstant results, a marked ketonuria being obtained in one of the four rats tested. These tests, though inconclusive, certainly do not suggest that an anomaly of pituitary secretion was present.

The foregoing studies had eliminated some of the possibilities in regard to the nature of the metabolic defect, but it was still impossible to decide whether the lipemia was due to some abnormal stimulus, hormonal or nervous, causing excessive mobilization of depot fat, or whether it was due to lack of some influence which normally controls the removal of fat from the blood. Our next step was to try the effects of various substances and biological principles which might possibly be of benefit either by controlling mobilization from the depots, by aiding the removal of fat from the blood or by stimulating fat combustion. These therapeutic essays all met with failure, as may be seen from the graph of the total blood lipids; nevertheless the negative results seem worthy of mention.

[7] These determinations were made by Dr. F. C. Dohan of the University of Pennsylvania to whom we wish to express our thanks.

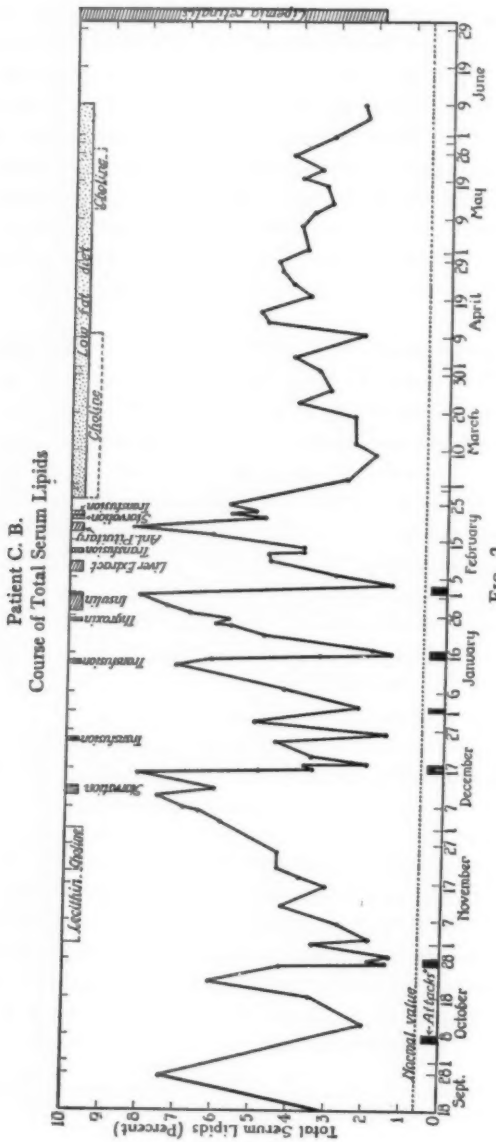
Patient C. B.
Course of Total Serum Lipids
Total Serum Lipids (Percent)
Normal value
Attacks
Lecithin Soybean
Normal Diet
Low Fat Diet
Creatine
Liver Extract
Transfusion
Ant. Pituitary
Thyroid
Insulin
Thiamin
Transfusion
Thiamin
Transfusion
Normal
Sept.
October
November
December
January
February
March
April
May
June

FIG. 2

Our first experiment was with lecithin. This was given because of the results obtained by Hershey, Best and their coworkers (25) in curing fatty liver in the insulinized depancreatized dog with lecithin, choline and betaine, and their similar more recent results with the fatty liver of rats induced by a high fat diet or by a diet rich in cholesterol. Egg lecithin was given by mouth—7 grams twice a day—from October 29 to November 20, 1935. During this interval the blood fat increased from 1.37 per cent to 4.35 per cent.

Choline was next tried since it seemed possible that there was not sufficient choline in the lecithin as given to be effective. Five grams a day of choline chloride were given, mixed with a chocolate drink to increase its palatability. During a period of ten days on this regime (November 20 to December 1, 1935) the blood fat increased from 4.35 per cent to 5.85 per cent.

Thyroxin was next tried, since hyperlipemia is often found in hypothyroidism and the converse in hyperthyroidism. Thyroxin was used rather than thyroid extract since, according to Leites (26), its effect is more rapid and is demonstrable by blood lipid determinations within twenty-four hours. A single dose of 2 mg. thyroxin was given intramuscularly on January 23, 1936. The blood fat level on that day was 5.62 per cent. On the following day it was 6.13 per cent and the day following that 5.73 per cent.

Insulin was next tried because of its known effectiveness in overcoming the lipemia of diabetes. Between January 27 and January 30, 1936, 5 units three times a day were given before meals. The blood fat rose from 6.77 per cent on January 27 to 7.33 per cent on January 29th. Two days after the insulin was discontinued the patient had a typical abdominal attack.

Liver extract seemed a logical material to try in view of the known relation between liver disease and lipemia. For four days (February 6 to February 9, 1936, inclusive) an intravenous injection was given of 5 cc. of a highly potent antianemic extract prepared by Dr. C. P. Rhoads. The blood fat at the onset of this period was 2.94 per cent; at the close, it had risen to 4.61 per cent.

An anterior pituitary preparation said to be rich in ketogenic hormone was kindly furnished us by Dr. C. N. H. Long. This material was injected intramuscularly in 5 cc. daily doses from February 17

to February 19th inclusive. During this time the blood fat rose from 6.10 per cent to 8.20 per cent. Fearing that an abdominal attack was imminent all food was stopped for a two day period following this, and the blood fat fell gradually without any unpleasant symptoms.

The suggestion was made by Dr. E. A. Park that transfusion might be of benefit, since it seemed possible that our patient was lacking in some principle present normally in the circulating blood. The re-

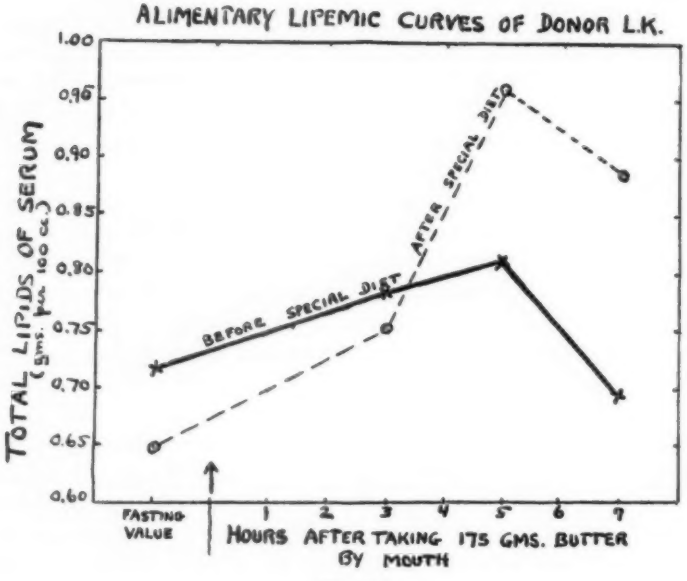

FIG. 3

sults of transfusion, though by no means conclusive, are nevertheless interesting. The patient was transfused four times. Her blood group was II (Moss). At the first transfusion (on December 24, 1935 from donor L. K.) 300 cc. of blood were given; two days later it was found that the blood fat had fallen from 4.48 per cent to 1.57 per cent. It was the only time such a low figure was obtained except immediately following an abdominal attack. The patient experienced no transfusion reaction. The same donor was used on a later occasion, this

time only 150 cc. of blood being given. Again a drop in blood fat took place, but it was not as striking as before. The blood fat before the transfusion was 4.76 per cent; on the following day it was 3.78 per cent and on the second day following it was 3.76 per cent. A transfusion from another donor (R. W.) apparently failed to benefit the patient at all. The blood fat was high (7.12 per cent) the day before it was given. The day following the transfusion a typical abdominal attack set in and the fat pursued its usual downward course. It was felt that the difference in the results obtained with the two donors might perhaps be explained by differences in their dietary habits. Donor L. K. was known to be a liberal fat eater, which was not the case with donor R. W. It has been observed by Bang (27), Leites (28) and others that animals maintained on a high fat diet develop a lowering of the alimentary lipemic curve. The same phenomenon was observed in the case of an infant studied (29) in our wards. Presumably, on a high fat diet the organism acquires an increased ability to remove fat from the blood. It seemed worthwhile to try to increase the beneficial effect observed with donor L. K. by adapting him to a really high fat diet for a two weeks' period and then transfusing with his blood. He was accordingly given a diet in which approximately 90 per cent of the calories were supplied in the form of fat. The diet was conscientiously taken, but within a few days the donor complained of great difficulty in getting it down. He developed a marked ketosis. After ten days on the diet it proved so nauseating and he felt so ill that he begged to have the experiment terminated and the transfusion given. This was accordingly done. To our disappointment the administration of 150 cc. blood failed to reduce the patient's blood fat at all; in fact it increased slightly—the figure before the transfusion being 4.81 per cent and that on the two succeeding days 5.65 per cent and 5.02 per cent respectively. This finding was, however, understandable when the alimentary lipemic curves of the donor—before and after his special diet—were analyzed. The alimentary lipemic curve had actually increased as a result of the diet; thus instead of increasing the donor's tolerance for fat, as we had hoped to do, we had apparently overshot our mark and had produced an intolerance to fat. It is unfortunate that the experiment could not be repeated keeping the donor's fat intake within his tolerance

and administering enough carbohydrate to prevent ketosis, but an opportunity to repeat it was not secured. We feel, however, that the results obtained, although they fail to provide conclusive evidence for a humoral factor influencing the level of blood fat, are at least suggestive of the presence of such a factor. On the occasion when our donor was suffering from fat intolerance his blood failed to benefit the patient, and on two occasions when he was in good health his blood did benefit her lipemia, more so when a large transfusion was given.

The studies mentioned were carried out between the latter part of September 1935 and the latter part of February 1936. During this five months' period the patient had had five abdominal attacks; this was in contrast to a two year period free from attacks before she entered the hospital. Although the ulcers on the leg had begun to show improvement in the middle of November and had healed completely the following month, the patient's condition was in other respects unimproved. Her weight was three pounds less than on admission. She had suffered from a few intercurrent infections during this period —an attack of impetigo in November with lesions on the face and hand, an attack of streptococcus sore throat in December with a mild delirious episode, and the following month she had had some dental repair work and an alveolar abscess had been drained. None of these episodes were sufficiently severe or prolonged to account for her failure to thrive, which we were inclined to attribute rather to the frequent abdominal attacks. For the increased frequency of these we could find no other explanation than that we had been feeding her more fat than she had been given at home. The hospital diet upon which she had been placed contained 50 grams of fat a day, and although exact information about her home diet was not available it seemed probable that it had been much less than this. We, therefore, attempted to study the effect of reducing the fat intake, and also to give choline a more extended trial.

For the next three months (2/26/36 to 5/27/36) the patient was allowed no more than 15 grams of fat a day. For the first part of this time choline was supplied; for a second period it was withheld and for a third period it was again supplied, but in larger quantity. The variations encountered in the blood fat were as follows:

Period I. (February 26–April 9). Choline 5 gm./day. Blood fat range 1.88–4.06 per cent.

Period II. (April 10–May 11). Choline omitted. Blood fat 2.19–4.97 per cent.

Period III. (May 12–May 27). Choline 9 gm./day. Blood fat 3.12–4.48 per cent. During these three months the blood fat remained well below the critical level. The patient had no further abdominal attacks and there was slow but steady improvement in her weight and general appearance. By the end of May she had regained the lost weight and had added $2\frac{1}{2}$ pounds to her admission weight. The liver and spleen remained palpable, being felt about 1 finger-breadth each below the costal margin after a deep inspiration, but they were far smaller than after an attack as is shown by the outlines in the accompanying photograph. We were unable to convince ourselves that choline was of any value; the entire benefit seemed to be due to the low fat diet. The fluctuations in the level of blood fat during this time were traced to variations in the fat intake from day to day. Although the upper limit was set at 15 grams a day there were days when as little as 6 grams of fat were ingested.

From May 27 to June 23, 1936 the fat intake was kept constant at 8 grams per day. Following this the blood fat fell below 3 per cent and remained between 2 per cent and 2.5 per cent until the time of discharge. A recurrence of psoriasis appeared in April and persisted throughout the greater part of May, the lesions being chiefly on the scalp and extensor surfaces of the extremities, only a few appearing on the torso. There was also an attack of follicular tonsillitis in the early part of June which was of brief duration. The patient was discharged on June 23, 1936, and sent home on a diet which included about 10 grams of fat per day.

She was seen again for a follow-up study on November 13th, 1936. She had been well since discharge, had had no further abdominal attacks and had passed the first summer in years without developing ulcers on the leg. She had been troubled only slightly during the summer by psoriasis of the scalp. Her weight had increased to $60\frac{3}{4}$ pounds and her height, which had remained practically stationary during her stay in the hospital, had increased to $52\frac{1}{4}$ inches. She was still below weight for her height, but less so than before. The

FIG. 4. Patient, C. B., showing the position of the liver and spleen immediately after an attack (dotted lines), as compared with their position after a prolonged period on low fat diet in which no attacks occurred (solid line).

liver and spleen were both palpable on deep inspiration, about as on discharge. Apparently the diet had been closely followed, for the blood fat was only slightly higher than when she left the hospital.

A further therapeutic experiment was carried out in the spring of 1937.[8] Since the beginning of our study the work of Dragstedt and his collaborators (30) had appeared who described the preparation of a new hormone—"lipocaic"—from pancreas which was far more potent than choline in curing the fatty liver of the depancreatized insulinized dog and which was presumed to act by increasing the combustion of fat. Through the courtesy of Dr. Dragstedt and Eli Lilly and Company a supply of this material was obtained and was fed to our patient in doses of 0.5 grams a day for a period of three weeks (May 15, 1937 to June 7, 1937). This brought about no reduction in the blood fat—the value being 2.70 per cent before the hormone was commenced and 3.26 per cent at the close of the experiment. Reports since then have stated that the patient continues in good health and still adheres to her low fat diet. A report in September 1937 stated that her appetite was excellent and that she had had no further skin lesions or abdominal cramps. At the age of thirteen years her height was 57 inches and her weight 68 pounds—a gain of $4\frac{3}{4}$ inches and of $7\frac{1}{4}$ pounds in ten months, a rate of gain which can be considered quite normal. At this time there was evidence of beginning puberty; the breasts were developing and some pubic hair had appeared.

Reports during 1938 state that the patient has continued to grow and develop satisfactorily. She has adhered faithfully to a low fat diet and probably receives no more than 10 grams of fat per day. There have been no more abdominal attacks or skin lesions of any kind. A blood sample obtained on July 14, 1938 showed total lipids 2.27 per cent, total cholesterol 146 mg. per 100 cc. and lipid phosphorus 12.1 mg. per 100 cc. Her first menstrual period was in October 1938. A sample of blood taken three weeks later showed the lowest fat content since her discharge from the hospital—1.7 per cent total lipids.

Some further information was obtained in regard to the patient's

[8] This was made possible by the coöperation of the family physician, Dr. John F. Lehman of Arthurdale, West Virginia, who supervised the medication and was kind enough to procure the blood samples for us.

family. On November 8, 1935 samples of blood were obtained from the parents and from the three siblings for lipid analyses. The values are shown in the accompanying table. It appeared that the younger brother, E. B., showed a condition quite similar to that of our patient, with a lipemia of 3.01 per cent, the increase being almost entirely in the neutral fat fraction. The slight elevation found in the case of the mother suggested that the condition might have been inherited from her. A few weeks later (November 26, 1935) we had an opportunity to examine the brother, E. B. His blood fat was then only slightly

TABLE 2

Serum lipids of the B. family

	AGE	DATE	TOTAL LIPIDS	TOTAL CHOLESTEROL	LIPID PHOSPHORUS	REMARKS
	yrs.		*(gm./100 cc. serum)**	*(mg. per 100 cc. serum)**	*(mg. per 100 cc. serum)**	
W. B. (father)	38	Nov. 8, 1935	0.58	159	7.3	
H. B. (mother)	39	Nov. 8, 1935	1.43	197	10.9	
J. B. (sister)	15	Nov. 8, 1935	1.14	161	8.7	
R. B. (brother)	13	Nov. 8, 1935	0.53	172	8.4	
E. B. (brother)	8	Nov. 8, 1935	3.01	209	12.2	
E. B. (brother)	8	Nov. 26, 1935	2.61	223	11.9	Lipemia retinalis. Palpable liver and spleen
E. B. (brother)	9	Nov. 12, 1936	2.02	201	10.3	
Patient		Sept. 18, 1935–Oct. 24, 1938	1.35–8.20	146–398	6.2–19.4	

* For normal values see table 1.

lower than before (2.61 per cent). It was found that his liver and spleen were easily palpable on inspiration and that his retinal vessels showed a definite lipemic appearance. At the time our patient was discharged from the hospital on a low fat diet the parents were told that it was probably not necessary for this brother to keep to a special diet since he had never had abdominal attacks and his blood fat was well below the level which had been critical in the case of our patient. However, they were told that if convenient it would probably be as well to give this brother any low fat foods they were preparing for her.

Possibly some degree of fat restriction was responsible for the fact that when his blood was next examined (November 12, 1936) there had been a further drop in the blood fat. The parents were questioned assiduously about any relatives who might have had symptoms similar to those of our patient, but no further information came to light.

DISCUSSION

We believe the evidence cited in the history justifies the interpretation that the hepatomegaly and splenomegaly in our patient were directly related to the lipemia. It is a question whether the skin lesions may be similarly explained. We have already referred to the literature (19) pointing to a connection between psoriasis and blood fat. This seems to have had its origin in the observation that in Germany during the great war at a time when there was a shortage of fat, many psoriasis patients showed improvement. The finding of a high blood fat in psoriasis appears to be an inconstant one and not particularly striking at that, and the reports of improvement by diminishing the fat of the diet have not been confirmed by a number of American dermatologists (31). In our patient we are inclined to question the relation between the lipemia and the psoriasis, particularly since a fresh attack of psoriasis made its appearance in April 1936 at a time when the blood fat was showing marked improvement.

There remains the question of the estival lesions which started as vesicles and went on to chronic ulceration of the leg. We are inclined to believe that these were impetiginous. Impetigo was said to be omnipresent in the small and rather primitive community in which the patient lived. The description of the onset of the lesions corresponded with that disease and several typical impetiginous lesions were seen shortly after she was first admitted to the hospital. Although impetigo is by no means confined to the summer months, it is certainly more prevalent then. It is a familiar scourge of summer communities, and sunburned skin seems to be relatively less resistent to it. The depth and the chronicity of the ulcerations were certainly not characteristic of impetigo and the recurrence of these lesions in one particular extremity remains to be explained. It seems probable that the peculiar localization was due to the persistance of infecting organisms—pyogenic cocci in all probability—at the site of an in-

interpreted as proof that it was caused by excessive mobilization. This reasoning seems to us unsound. Cord section in any case would reduce mobilization and lessen the load on the liver, but one cannot tell from such an experiment whether mobilization has been reduced from an excessive to a normal level (which a normal liver can then take care of) or from a normal to a subnormal level (which a damaged liver could then take care of). Likewise, the accumulation of an excess of neutral fat in the liver cells fails to tell us whether this is due to an excessive load or a diminished capacity. A similar fallacy lies behind attempts to establish the existence of hypermobilization by identifying the iodine value of the lipemic blood fat with that of depot fat. Similarity of the iodine values does not tell whether an excess of depot fat in the blood is due to excessive mobilization or defective removal. In some instances the lipid partition in the blood is of help. Thus we know that depot fat is practically all neutral fat. In every lipemia some increase in cholesterol esters and phospholipids is likely to occur, but if the cholesterol esters play a prominent part in the lipemia, as is the case in nephrosis, for example, one can be reasonably sure that some factor other than excessive mobilization is at work. Unfortunately, the absence of a marked cholesterolemia does not permit us to draw the converse conclusion that excess mobilization is present. In the case of our patient it is clear that we have no reliable means of excluding hypermobilization of depot fat. Our hope of reaching a definite conclusion lies in excluding other possibilities or establishing some one of them.

Can we establish the existence of difficulty in fat combustion or transformation, or in the removal of fat from the blood? Our studies of the respiratory metabolism gave no indication of inability to burn fat; the normal ketosis on starvation indicated fat combustion. One transformation of fat, attributed to the liver, that can be tested for is the synthesis of cholesterol esters. As was first demonstrated by Thannhauser and Schaber (40), disease of the liver may result in a marked decrease of the ratio $\frac{\text{ester cholesterol}}{\text{free cholesterol}}$. Definite evidence of such an "*estersturz*" was obtained in our patient indicating that the transformation of fat in the liver was not occurring in an altogether normal manner. Granting, however, that the transformation of fat

in the liver is impaired, it does not follow that this is sufficient to account for the lipemia. Such a degree of *esterstarz* is in fact not uncommonly found in the complete absence of lipemia, and indicates that some further explanation of the lipemia must be sought.

There remains the question of a defective mechanism for removing fat from the blood. This possibility is not mentioned, so far as we are aware, by others who have discussed the subject of lipemia. The general view has been that hepatic injuries produce only the obstructive type of lipemia. It seems to us necessary to consider that the liver performs two distinct functions here, instead of just one. Although in certain cases of lipemia, such as those due to phosphorus poisoning, the liver may be found extremely fatty (enough so to suggest a damming back of fat in the blood), under other conditions this may not be the case. Lipemia may be found in the presence of necrotic changes in the liver with a minimum of fat infiltration. It is difficult in the latter case to think of the lipemia as caused by damming back of fat. One must assume the failure of some active mechanism for the removal of fat from the blood by the liver cells.

Is the condition in our patient a damming back of fat in the blood due to the liver being filled to capacity with fat, or is it a failure of some active mechanism for removal of blood fat by the liver? The former hypothesis does not seem in accord with the facts. In the period following a crisis the liver was found to be decreasing in size at a time when the blood fat was rising. After such a shrinkage in size, it is reasonable to assume that the liver contained somewhat less fat than its maximum capacity, yet in spite of this potential storage space, fat continued to accumulate in the blood. The facts would seem to point to failure of an active mechanism for removing blood fat. The failure is not a complete one, for it would appear that the mechanism can be stimulated to activity by a sufficient concentration of blood fat. In this connection we should like to call attention to certain facts reported in the literature which point to the existence of some such mechanism for removing blood fat—a mechanism which is sometimes sluggish and can be stimulated by a load. Van Slyke and his collaborators (41) and more recently Achard (42) have called attention to the vagaries of the alimentary lipemic curve and to the fact that in certain individuals a paradoxical hypolipemia follows the

ingestion of fat. In diabetes, Bloor (43), Leites (44) and others have reported similar paradoxical responses to the ingestion of fat; they were inclined to regard them as features of the disease rather than as peculiarities that might be found in normal individuals. We have called attention above to the fact that the alimentary lipemic curve can be conditioned by the diet (27, 28, 29). It is a question whether the removal of blood fat by the liver is due to an intrinsic cellular mechanism or to one that is subject to humoral influences. The observations of Lombroso (45) suggest this latter view. He found that a normal dog's liver perfused with blood would remove the fat from it whereas the liver of a depancreatized dog failed to do so. The effect was attributed to the influence of insulin on the liver, since the liver of the insulinized depancreatized dog behaved like that of the normal dog. The observations we have described in our patient following transfusion support the view that a humoral mechanism is concerned in the removal of blood fat; they also suggest that the difficulty in her case lay in a deficiency of such a humoral factor, but they do not point to insulin as the factor concerned. It is of course possible that the reduction in lipemia which we observed following transfusion and that observed by others after fat administration are due to inhibition of depot mobilization rather than stimulation of a removal mechanism, but this seems to us rather improbable.

The failure of our specific therapeutic measures is in harmony with the view that it is the removal mechanism which was at fault in our patient. Choline and presumably the "lipocaic" factor of Dragstedt appear to act by stimulating the utilization of fat in the liver. The fat metabolism hormone of Anselmino and Hoffmann is alleged to act in a similar fashion. We are probably not justified in drawing conclusions as to the pathological type of our lipemia from the failure of insulin and thyroxin therapy inasmuch as doubt prevails as to the mechanisms by which these agents affect fat metabolism. Both these agents appear to exert their influence in a highly specific manner —that is, insulin seems to affect only lipemias due to disturbed carbohydrate metabolism and thyroxin those due to hypothyroidism, so that we can only conclude that these were not the difficulty in our case.

One further question remains to be discussed—the relation between

the condition in our patient and the so-called diseases of lipid storage—the "lipoidoses." The literature on the accumulation of fat in various organs is very confusing, owing to frequent failure to distinguish between several distinct pathological processes. There can be little doubt of the existence of the condition spoken of by pathologists as "fat phanerosis."[9] In this state, damage to a tissue causes the fat previously present in invisible form to become visible in the form of droplets and stainable by fat stains. The quantity of fat in the tissue is not increased, nor is there deposition of fat from outside sources judging by the chemical characteristics of the fat. In all probability the disturbance is due to abnormal enzymatic processes which cause lipoprotein combinations or other complex lipids to be broken down. The term "fatty degeneration" can properly be applied to this process and to this alone. A second and far more common disturbance is the accumulation in the *parenchymatous* cells of organs, notably the liver, of fat which has the chemical characteristics of depot fat. The origin of this fat outside the tissue in question has been repeatedly demonstrated (4, 49), and the term "fatty infiltration" seems most appropriate. A third type of disturbance may occur when any lipemia reaches a sufficient degree; an accessory mechanism for removing fat from the blood is brought into play and the *phagocytic* cells belonging to the reticuloendothelial system—notably the Kupffer cells of the liver and the macrophages of the spleen—engulf the fat in particulate form.[10] A liver of this type, which for want of a better term we may call "fat phagocytosis," may contain by chemical analysis enough fat to be classed as a fatty liver, but it is important to distinguish it from that type due to infiltration of the parenchymatous cells. In the true "obstructive lipemia" in which the liver cells are loaded with fat, there may also be fat phagocytosis. But in the lipemias due to a defective removal mechanism the liver cells may show no increase in fat, fat being found almost exclusively in the Kupffer cells. Such a condition has been encountered not infrequently in diabetes (52). Fat

[9] This condition has been produced experimentally by Simms (53).

[10] Additional compensatory processes that may under certain circumstances play a rôle in reducing lipemia are: excretion of fat into the intestine in abnormal quantities, lipuria, and fat emboli in various organs. In general these are to be regarded as pathological accidents rather than physiological mechanisms.

phagocytosis can be produced in animals (46) by overloading the circulation with emulsified fat. Clinically, the condition is characterized by enlargement of the liver and spleen; the splenic enlargement is, however, much more striking than the hepatic, for phagocytic cells are more abundant in the spleen than they are in the liver. An analogous state of affairs—with phagocytosis of lipids other than neutral fat—is believed to occur in the so-called diseases of lipid storage—Gaucher's disease, Niemann-Pick disease and generalized xanthomatosis. The case for lipid phagocytosis is, however, not proved here. Thannhauser (47) has pointed out that evidence of abnormal quantities of these lipids in the blood is wanting and it may be that they are produced by the phagocytic cells themselves, due to some derangement of their metabolism. With the merits of this controversy we are not concerned; we are, however, interested in the question of whether the phenomenon of fat phagocytosis plays any part in the picture presented by our patient. The fact that the spleen of our patient remains enlarged suggests that such is the case; the more striking hepatic enlargement indicates, however, that the process in the liver is not confined to the Kupffer cells. It seems probable that a microscopic examination of the liver of our patient would have revealed aggregations of neutral fat in the liver cells as well as in the Kupffer cells.

Summing up, then, our conclusions in regard to the origin of the lipemia, we may say that a lipemia of plethora is out of the question. We have no evidence for hypermobilization of fat from the depots, though this possibility cannot be definitely excluded. We find no difficulty in fat combustion, but we do have evidence of difficulty in the transformation of fat in the liver, in the form of an abnormal ratio of free to combined cholesterol. The lipemia does not seem to be caused by damming back in the blood of fat by a liver which is filled to capacity. The root of the difficulty seems rather to be a sluggish mechanism for the removal of fat from the blood by the liver cell, a mechanism that is stimulated by a sufficient load. There is some indication that a humoral factor is concerned in this mechanism. A secondary phenomenon which has apparently been brought into play in an attempt to take care of the lipemia would seem to be the

phagocytosis of fat by the Kupffer cells of the liver and the phagocytes of the spleen.

We have attempted to find in the literature reports of cases similar to ours, but have not succeeded in doing so. There are various reports, such as that of Moro (50) of unexplained periodic abdominal crises in which observations of the blood fat were not made. It is possible that some of these may have been the same condition. Instances of acute hepatomegaly associated with abdominal pain have been observed in juvenile diabetics—usually those poorly regulated, and have been attributed to sudden accumulation of fat in the liver with stretching of the capsule. Dr. James Bordley III has called our attention to an interesting case of this kind (I.K., Unit No. 100255) observed on the medical wards of the Johns Hopkins Hospital in 1929. The abdominal symptoms and the presence of fever and leucocytosis suggested gall bladder disease; on opening the abdomen the gall bladder and bile passages were found quite normal, the only positive finding being an enlarged liver which appeared to be fatty although tissue was not excised for biopsy. Cases similar to this have recently been described by Marble, White, Bogan and Smith (54). In none of these, however, was the nature of the hepatic enlargement proved by biopsy, nor was the enlargement correlated with disappearance of fat from the blood.

Opitz (20), in describing his patient with an unexplained lipemia, mentions spells of weakness and sweating and abdominal pain—prolonged and unrelated to meals. No details are given as to the onset and termination of such symptoms nor of any relation between them and the blood fat; the abdominal pain was said to have followed trauma in the first instance. Bernard's patient (7) sought medical advice because of sharp pains over the liver, but these appear to have been constant. It is of interest that a fat-poor diet relieved the pain and reduced the lipemia and the size of the liver. Björum (48) described the familial incidence of fatty liver, but abdominal attacks were not mentioned nor were observations made on the blood fat. Since our preliminary report appeared, however, we have had letters from two physicians[11] telling about patients known to them who

[11] Dr. T. F. McNair Scott and Dr. Thomas B. Cooley.

presented marked similarities to our case, though not identical in all details. An abstract of a somewhat similar case has also appeared in the literature (51). It is probable that familiarity with the picture will result in the recognition of other cases.

SUMMARY

In a girl of eleven years there was found extreme lipemia—due primarily to neutral fat—associated with hepatomegaly, splenomegaly, psoriasis, peculiar ulcerations of the skin and malnutrition. Periodic acute attacks of abdominal pain occurred which were accompanied by a sudden reduction of blood fat, enlargement of the liver and spleen and engorgement of the abdominal veins. There was evidence that the disorder was familial.

The condition was not improved by lecithin, choline, thyroxin, insulin, "lipocaic" or anterior pituitary therapy. It could, however, be in large measure controlled by a low fat diet. Some evidence was obtained of a beneficial effect of transfusion.

The various types of disturbance which may give rise to lipemia are discussed. It is suggested sat the condition described is due to a defective mechanism for removal of blood fat by the liver—a mechanism in which a humoral factor appears to be concerned.

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FOLLICULAR LYMPHOBLASTOMA AND A RELATED FORM OF LYMPHOSARCOMA

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In the pages to follow five cases of follicular lymphoblastoma are reported; and in addition, four related cases which have presented puzzling clinical and pathological pictures are described. These have heretofore been roughly grouped with the other lymphosarcomata, but they have a sufficiently uniform pathological picture and are similar enough clinically to allow differentiation into a special group. Stress is laid on the unusual features of the cases, particularly, in an attempt to draw clinical-pathological correlations. It has generally been agreed that the usual case of follicular lymphoblastoma conforms to a fairly definite mold; variants from this typical picture will be discussed, and the widespread manifestations of the disease emphasized. The entity of follicular lymphoblastoma probably belongs somewhere in the family of lymphosarcoma; it differs from other lymphosarcomata in a number of respects, however, and it is these points of differentiation which constitute the characteristic clinical syndrome. Briefly, follicular lymphoblastoma has been described as a relatively benign disease of the lymph glands and spleen with a characteristic pathological picture, with little or no constitutional symptomatology, a normal blood picture, and marked radio-sensitivity. On the other hand, one sees rare cases of malignant lymphosarcoma with splenomegaly, and this group should not be confused with follicular lymphoblastoma.

THE CLINICAL-PATHOLOGICAL CONCEPTION OF FOLLICULAR LYMPHOBLASTOMA

Since the first emphasis placed upon follicular lymphoblastoma as a clinical entity by Brill, Baehr, and Rosenthal in 1925 (4), scattered reports, mostly pathological, have appeared in the literature.

It has been pointed out in retrospect that the first recorded clinical case of follicular lymphoblastoma was that of Becker in 1901. The clinical picture was much like that usually described in this disease, and a biopsy taken five years after the onset is said to have shown "simple hyperplasia." In 1925 Brill, Baehr and Rosenthal (4) reported two cases which at that time they called splenomegalia lymphatica hyperplastica; both were given roentgen therapy, and one was subjected to splenectomy. On the basis of the dramatic response to the former mode of treatment the authors were inclined to regard the process as a benign one. In 1927 Baehr and Rosenthal (3) reported a total of six cases, and by that time had had sufficient opportunity for observation to revise earlier impressions and to apply the term "malignant lymph follicle hyperplasia" to the picture. They at that time elucidated the salient features which seemed to distinguish follicular lymphoblastoma from other members of the large group of lymphoblastomata. They stressed the following features: generalized lymphadenomegaly and splenomegaly due to hyperplasia of the germinal centers of the lymph follicles; essentially normal blood picture; absence of cachexia; tendency to serous effusions as a result of pressure by enlarged lymph glands; absence of involvement of tonsils or gastrointestinal lymphatics; unilateral exophthalmos as a result of infiltration of the lacrimal gland. In this same year Symmers (12) reported three cases, all following essentially the same pattern; he felt that the clinical picture was so like Hodgkin's disease, chronic lymphatic leukemia, "pseudoleukemia," and lymphosarcoma that it was distinguishable only by biopsy and by the benign course. The pathological picture he then believed to be much more akin to the reaction of lymphatic tissue to inflammatory and toxic conditions than to malignant processes. In 1932 Baehr (1) again reported his series of cases, and by this time they numbered nineteen. He stressed the dramatic response of follicular lymphoblastoma to roentgen therapy; he also reported a simple analysis of his series, and recorded the following data: age 20–68 years, average 42 years; sex, male 13, female 6; lymphadenopathy, general 15, local 4; clinically detectable splenomegaly, present 12, absent 7; unilateral exophthalmos 4; X-ray response, good in 14; duration, 7 dead in an average of 5 years, 9 months; 8 living, an average of 5 years.

Baehr, Klemperer and Rosenthal in 1931 (2), and Klemperer in 1934 (7) further discussed the pathological picture, emphasizing in particular the later malignant phase, thought it a lymphosarcoma or a link between lymphosarcoma and lymphatic leukemia. Klemperer (7) reported that one of the original cases of Baehr, Rosenthal and Brill subsequently had developed the blood picture of chronic lymphatic leukemia. Between 1931 and 1937 scattered cases were reported, one by Ewing and Fein (6), two in the Cabot Case Records of the Massachusetts General Hospital (5), and in 1933 Rosenthal, Harris, and Kean (9) reported ten cases of follicular lymphoblastoma treated with X-ray, of the total of 156 cases of malignant lymphadenopathy of all kinds so treated at the Mt. Sinai Hospital in New York City. Ross (10) reported a case in 1933 and Scott and Robb-Smith one in 1936 (11).

Searching microscopical analysis had not been made until Symmers published his report in 1938 (13). In this paper a noteworthy analysis of the minute pathology was made the basis of an attempt to subdivide follicular lymphoblastic tumors. His first division comprises the cases in which there are no microscopical changes other than an increase in the number and size of the lymph-glandular and splenic lymph follicles, the increase in size of the latter being brought about by great hyperplasia of the germinal centers. The second division includes those cases in which there is, in addition to the simple increase in size and number of follicles, either the coincidental or subsequent finding of the pathological picture of some other related disease. In this subdivision are described: (a) transformation to a polymorphous-cell sarcoma of the lymph follicles; (b) association with Hodgkin's disease; (c) association with lymphatic leukemia; (d) association with late necrotic changes in the follicles. Symmers reports six new cases of follicular lymphoblastoma, and one case in which he believes that the picture has been changed by the occurrence of "necrotizing folliculitis." He also reports 18 other cases which show either "transformation" to polymorphous cell sarcoma of lymph follicles (7 cases) or association with Hodgkin's disease (7 cases) or lymphatic leukemia (4 cases).

In November 1938 Robb-Smith (8) published a paper classifying the various diseases of the lymph glands of unknown etiology using

Pullinger's modification of Maximow's hypothesis of the pluripotentiality of the undifferentiated mesenchymal cell. He calls them all "reticuloses" and divides them into follicular, sinus or medullary reticulosis according to the place of origin of the characteristic cell. He describes one case under the term lymphoid follicular reticulosis in which "The enlarged follicles consist of a central area of cells resembling lymphoblasts in which there are no active mitoses, reticulum cells nor histiocytes, and a rim of small lymphocytes with no intermediate forms between them." He makes a definite distinction between "progressive hyperplasias" and "neoplasias" but states that blastomatous change has been observed in both forms of follicular reticulosis.

A brief review of the salient pathological features reveals certain outstanding points. The site of origin of these tumors is in lymphatic structures, almost anywhere in the body, but, as stressed by Baehr and Rosenthal, they have never been seen in the tonsil or the lymthatics of the gastro-intestinal tract. Whether the process arises in one place or in many places simultaneously is not certain. A number of the recorded protocols, including most of our own, give as the initial complaint, "swelling in the neck." In most instances when the paients are first seen there is general lymphadenopathy. The usual glands involved are the superficial ones, but a number of the cases present clinical and pathological evidence of involvement of deep gland groups, at times massive and far exceeding in gravity the more evident superficial tumors. The involved glands are firm, usually insensitive, and are discrete until the final infiltrative phase is reached. They are greyish and solid on section. In the late stages the glands lose their discrete nature when the capsules are invaded. The spleen, in all instances, partakes of the process. In presents all degrees of enlargement, and has been reported to reach a weight of 1800 gms. Its appearance on cross section is a characteristic one, for the follicular hyperplasia in the Malpighian bodies results in a grossly visible peppering of the surface with tiny greyish tumors.

The microscopic changes are the ones which distinguish this entity from the related lymphoblastomata. In the early stages, and indeed until the terminal stages, follicular structure is maintained, in contradistinction to lymphosarcoma and lymphatic leukemia wherein gland structure is replaced by a homogeneous mass of tumor cells. The

essential change in follicular lymphoblastoma is a tremendous hyperplasia of the germinal centers of the lymph follicles. Until the late stages the follicles are delimited by narrow zones of small mature lymphocytes. Later the lymphoblasts of the proliferating germinal centers may destroy this follicular structure, but even then one can find strands of the smaller cortical cells remaining here and there. In this stage the capsule may be invaded. A somewhat similar microscopic picture is seen in the reaction of lymphatic tissue, especially in children, to benign infectious or irritative processes, for here also there occurs follicular hyperplasia of great degree. Such material taken at biopsy may well prove misleading.

PRESENTATION OF CASES

Group I

The first group includes five cases of follicular lymphoblastoma. Unfortunately there were no autopsies on the three cases now dead, but on the basis of biopsy alone one can usually distinguish the terminal phase from the relatively benign phase.

Case 1. (Unit no. 46325.) A white man aged 39 was first seen at the Johns Hopkins Hospital on November 15, 1932, where he entered on the service of Dr. Henry M. Thomas, Jr. His past history was singularly unenlightening. He had first noted enlarged axillary glands in April 1932. When examined at this time by Dr. Thomas, he was found to have enlarged axillary and inguinal glands, one palpable epitrochlear gland, a greatly enlarged liver and a spleen that reached to the umbilicus. Blood counts taken in April did not differ materially from those to be reported below. Biopsy of a lymph node was performed at the Union Memorial Hospital, Baltimore, in April 1932, and showed great enlargement of the individual lymph follicles and great increase in number of follicles, each rimmed by a narrow zone of small lymphocytes, and filled with large germinal cells. In May a large mass was first indefinitely felt below the liver. He was given X-ray treatment prior to entrance to the hospital, and the lymph nodes and spleen had responded by marked diminution in size, for a short time. On admission to the hospital he appeared somewhat below par, and a little pale. There was generalized enlargement of the superficial lymph nodes, and the glands were firm, discrete, not tender. There was bilateral hydrothorax. The spleen extended two finger-breadths below the costal margin; it was firm and not tender. The liver edge reached four finger-breadths below the costal margin. There was a huge abdominal mass thought to be made up of mesenteric lymph nodes.

Laboratory examinations: Red blood cells 4,800,000, hemoglobin 80 per cent, white blood cells 8,000, with polymorphonuclear neutrophiles 73 per cent, large

lymphocytes 12 per cent, small lymphocytes 9 per cent, eosinophiles 6 per cent. Kidney function was normal, as were blood nonprotein nitrogen, sugar, calcium and phosphorus. Plasma proteins totaled 4.01 gm. per 100 cc., cholesterol 143 mg. per 100 cc. The Wassermann reaction was negative. Thoracentesis yielded chylous fluid with considerable fat and a cholesterol content of 93 mg. per 100 cc.

There were frequent subsequent admissions for thoracentesis. On his last admission from March 6, 1933, until his death on May 23, 1933, there was persistent rapid accumulation of the same chylous fluid in the chest, and there was a marked increase in the size of the superficial lymph nodes. The spleen was definitely reduced in size as the result of radiation. There was progressive anemia

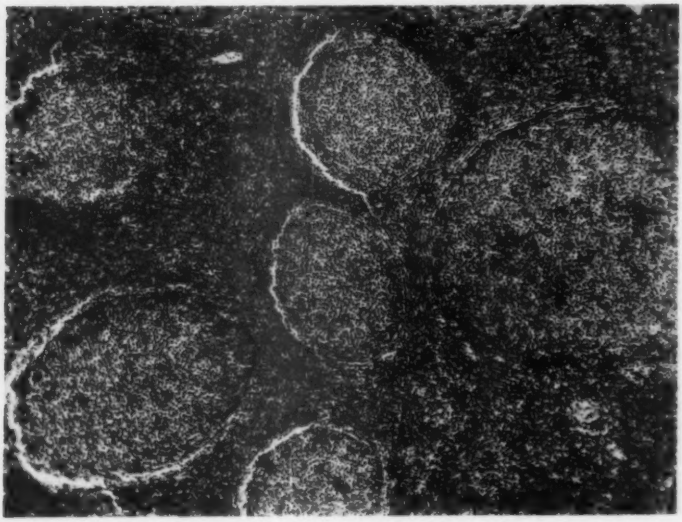

FIG. 1. (CASE 1). FOLLICULAR LYMPHOBLASTOMA. LYMPH NODE. ×60

before death, and, terminally, a few "immature myelocytes" appeared in the blood stream. For the last two months only, he ran a spiking fever; the remainder of the course was afebrile. No biopsy was done in the terminal phase and no autopsy was obtained.

Case 2. (Unit 76973.) A white male aged 30 entered the Johns Hopkins Hospital on January 22, 1937, on the service of Dr. Henry M. Thomas, Jr., and remained until April 21, 1937. His initial complaint was of "swollen glands." He had first noted glandular enlargement in the neck and left axilla a year before but had paid little attention to it until persistent fever started in July 1936. The past history was negative. Physical examination, aside from the evidences of anemia and weight loss, showed nothing but considerable enlargement of the

posterior cervical, submaxillary, and axillary lymph nodes, and a spleen that extended to the level of the umbilicus. The liver was not enlarged.

Laboratory examinations: Red blood cells 2,960,000; hemoglobin 7.4 gm. per 100 cc.; white blood cells 4,000; mean corpuscular volume 80; mean corpuscular hemoglobin 25; mean corpuscular hemoglobin concentration 32. Icterus index 7. Differential: juvenile neutrophiles 15 per cent, polymorphonuclear neutrophiles 57 per cent, eosinophiles 1 per cent, small lymphocytes 4 per cent, monocytes 23 per cent. The monocytes had a blue-grey cytoplasm (Wright stain), finely granular with an occasional azurophil granule, and many vacuoles; the nuclei were lacy. Platelets numbered 80,000 to 107,000. Blood nonprotein nitrogen and sugar were normal, and the Wassermann reaction was negative. Urine and stool studies were negative. Uric acid and heterophile antibody determinations were not made, and a basal metabolism test was not done because of persistent fever. X-ray of the chest showed normal mediastinum.

He was given roentgen therapy which had to be discontinued because of the leukopenia of 1,300 which resulted. He was given pentnucleotide without any recognizable effect, and repeated transfusions with only temporary benefit. Numerous blood studies consistently showed the same general changes. He died six weeks after leaving the hospital, anemia having been progressive and fever spiking. No autopsy was done. Total X-ray was 555 roentgen units to left axilla, 185 to right axilla, 148 to neck, 133 to spleen. A gland was taken from the right axilla on January 27, 1937.

Pathologic report by Dr. K. Pickrell: "The acetone and permanent sections show essentially the same thing, namely an axillary lymph node which is almost completely occupied by a tumor mass that is composed of rather large, pale-staining cells, which in practically every instance contain nuclei and in some places several nucleoli. The cytoplasm is extremely scanty and the limiting membranes indistinct. Interspaced between these large, pale-staining cells there are scattered small, amply-staining lymphocytes. Although the total architecture of the lymph gland has been entirely obliterated, it is now replaced by large follicles which are again composed of the previously described large pale cells which at the periphery of the follicles are arranged in a circular manner and in some instances are surrounded by smaller, more deeply staining lymphocytes. The tumor has a very invasive character, having ruptured through the capsule in many instances and has now extended out into the fat which is attached. In many cases this tumor mass can be seen invading directly into the walls of blood vessels; no cells are seen to pierce the walls, however. There are many bizarre nuclei and mitotic figures."

Case 3. (Unit 66895.) A white male aged 50 years entered the Johns Hopkins Hospital on the service of Dr. Lay Martin on July 6, 1937, remained until August 18, 1937, and died without autopsy. His entering complaint was "gland enlargement." For many years he had noted that the glands in his neck would enlarge with colds. Since 1933 the inguinal glands had enlarged to the size of a small egg, and had undergone transient changes in size. Since 1934 he had known of en-

larged epitrochlear and axillary lymph nodes. A biopsy of a cervical node in 1933 was said to have shown "nothing malignant." Five months before admission he had had malaise and general aching for a month, then developed a non-productive cough which had persisted until entrance to the hospital. There had been some abdominal distention with alternating diarrhea and constipation. There had been no fever. There had been a fifteen-pound weight loss in the last five months, during which time he had noted night sweats, cramps in the legs, and pitting edema of the feet. The past history was non-contributory save that he had had quinsy when about 21, and from 14 to 18 years of age had had growing pains.

On physical examination he was seen to be thin and of sallow complexion. The eyes were a bit prominent. The tonsils were huge, and very firm. There was considerable enlargement of the anterior cervical lymph nodes, less of the posterior cervical and epitrochlear groups. The right inguinals were very large, and matted. The sternum and anterior part of the right seventh rib were tender. The veins of the arms were prominent. The spleen was just palpable.

Laboratory examinations: Red blood cells 4,430,000, hemoglobin 13.0 gm. per 100 cc. Volume of packed red blood cells 39.5. Corrected sedimentation rate 18.0 mm. in one hour. Mean corpuscular volume 89, mean corpuscular hemoglobin 29, mean corpuscular hemoglobin concentration 33 per cent. White blood cells 4,800. Differential: juvenile neutrophiles 8 per cent, polymorphonuclear neutrophiles 58 per cent, eosinophiles 4 per cent, basophiles 1 per cent, small lymphocytes 20 per cent, monocytes 9 per cent. Nonprotein nitrogen 44 mg. per 100 cc. Fasting blood sugar 82 mg. per 100 cc. Uric acid 11.2 mg. per 100 cc., and 11.4 mg. per 100 cc. The Wassermann reaction was negative. Heterophile antibody titre 1:1. The basal metabolic rate was +36 per cent, and +48 per cent. The urine was negative except for a small amount of albumen.

He was given roentgen therapy from July 12th to July 21st, 1937, 1512 roentgen units to the right inguinal region, 648 roentgen units to the left inguinal region, 432 roentgen units to the right axilla and 432 roentgen units to the left axilla.

He remained afebrile, but rapidly became weaker. White blood cells dropped to 3,850. He developed hepatomegaly and jaundice with a biphasic Van den Bergh of 6.5 mg. bilirubin per 100 cc., and died following gastric hemorrhage.

A lymph gland, excised five days before X-ray treatment was started, showed marked increase in size and number of the individual lymph follicles; the huge germinal centers were composed of large, rather pale cells of embryonic character, and the cortical rinds of mature lymphocytes were quite thin. Cells of the character of those seen in the germinal centers seemed to have broken through the cortical zone in many places to invade the interstitial tissue of the lymph node.

Case 4. (Unit 127851.) A white man aged 42 entered the Johns Hopkins Hospital on January 6, 1938, on the service of Dr. Samuel Whitehouse, complaining of swollen ankles and neck. For the past ten years he had had post-prandial acid eructations and on several occasions prior to 1935 had had tarry stools. He had noticed exertional dyspnea for several years, but edema of the ankles had only appeared five weeks before admission, at first only at the end of the day, later

constantly. About four to five weeks before admission he had first noted painless swellings on both sides of the neck. He maintained that his abdomen had been increasing in size for the preceding ten years.

Physical examination: Blood pressure was 165/100. He was pale. The abdomen was hugely distended. There was slight enlargement of the neck veins. There was dental caries. The tonsils were large and infected. The thyroid was diffusely enlarged. There were great masses of insensitive, slightly matted nodes on the left side of the neck, and in both supraclavicular fossae. The axillary glands were the size of marbles. There were enlarged inguinal and left epitrochlear nodes. The diaphragm was very high, breath sounds were everywhere very loud, and there were atalectatic râles at both lung bases. The heart was normal except for its transverse position. The abdomen was greatly distended, with visible veins coursing over its surface. There was percussion flatness in an irregular area 22 x 30 cm. in diameter, involving the left flank from the costal margin to the pelvic brim and extending medially to the midline. A hard irregular mass was palpable in this area. On rectal examination there was seen to be a protruding rosette of internal hemorrhoids, and deep in the pelvis a hard, rough edge was palpable.

Laboratory examinations: The Wassermann reaction was negative. Blood nonprotein nitrogen 85 mg. per 100 cc., fasting sugar 87 mg. per 100 cc. Uric acid 8 to 9 mg. per 100 cc. Red blood cells 3,800,000. Hemoglobin 12 gm. per 100 cc. White blood cells 7,050. Differential: juvenile neutrophiles 6 per cent, polymorphonuclear neutrophiles 71 per cent, eosinophiles 2 per cent, small lymphocytes 19 per cent, monocytes 2 per cent. The basal metabolic rate was +23.5 per cent. Flat X-ray plate of the abdomen, and gastro-intestinal X-ray pictures showed a large mass displacing the intestines to the periphery, but not itself attached to them. Chest X-ray plate was negative. Blood counts remained the same with a drop in the white count to about 5,000 after X-ray treatment was started.

From January 11, 1938 through April 9, 1938, he received 918 roentgen units to the upper abdomen, 108 to the lower back, 810 to the mid-abdomen, 756 to the left side of the neck, 1512 to the right side of the neck, 1278 to the left chest, 1278 to the right chest, and 410 to the right pelvis. He was practically afebrile.

A gland in the neck was removed for study on January 7, 1938, four days before roentgen therapy was started. Dr. Vandergrift's pathological note on this gland was as follows: "Acetone and permanent sections show lymph nodes containing a great number of large follicles characterized by large germinal centers and a relatively small amount of surrounding lymphocytes. The sinuses are small, inconspicuous, and practically empty of cells. There is a diffuse increase in the parenchymal elements associated with the decrease in the sinuses. In the pulp there is a large number of lymphoblast-like cells."

The patient was discharged from the hospital in February and completed his course of X-ray treatment while out of the hospital. He returned on August 23, 1938. He had remained fairly well until July, since which time he had had a cough of progressive severity, with mild chest pain, and some thick sputum. The edema

of the legs, which had been much less, had become much worse in the preceding few days. He had had occasional gross hematuria.

On examination he appeared to be pale. Tonsils were now small. No axillary or inguinal nodes were palpable and only a few small soft cervical glands. The diaphragm again seemed very high, and there were a few musical basal râles. There was some pain on pressure over the left lower ribs. The heart was enlarged and presented frequent extrasystoles. The blood pressure was 180/100. The abdomen was distended and tympanitic throughout. The tip of the spleen was just palpable. The huge abdominal mass was no longer definitely felt, but medial to the palpable right kidney there was felt a small irregular mass.

Laboratory examinations: Red blood cells 2,870,000, hemoglobin 8.7 gm. per 100 cc. Volume of packed red cells 24.8. White blood cells 2,850. Differential: juvenile neutrophiles 8 per cent, polymorphonuclear neutrophiles 54 per cent, eosinophiles 2 per cent, small lymphocytes 26 per cent, monocytes 8 per cent. Nonprotein nitrogen 78 mg. per 100 cc., creatinine 5.6 mg. per 100 cc., serum phosphorus 9.1 mg. per 100 cc., phosphatase activity 3.4 Bodansky units. Total protein 5.8 gm. per 100 cc. with albumen/globulin ratio of 54/46. The chest plate showed enlargement of the heart since the previous examination, with marked passive congestion of the lungs.

Thoracenteses were attempted unsuccessfully. One transfusion of 500 cc. was given, and intensive liver therapy was carried out. Sternal marrow was obtained by biopsy and was entirely normal. The hypertension was maintained, the urine on numerous occasions showed a small amount of albumen; its specific gravity varied between 1.008 and 1.012, could not be concentrated further. From August 27th until September 13th the patient was given a total of 420 roentgen units to the right side of the neck and 420 roentgen units to the left side of the neck. Circulatory compensation was regained, but the other findings did not change. He was discharged on October 14, 1938, much improved.

Case 5. (Unit 148289.) A white male aged 39 years entered the Johns Hopkins Hospital on August 7, 1938, on the service of Dr. A. Murray Fisher, with a complaint of pleurisy, and remained until August 21, 1938. His past history was negative except that he had known of swollen glands in his neck for about seven years. The glands had not increased in size, and had given no trouble. He had been active and well until nine weeks before entrance when he developed pleurisy on the left side. He consulted a doctor who discovered an enlarged spleen and "fluid in the chest." A cervical lymph node was excised for biopsy. He was given twenty-three X-ray treatments, reducing the size of the spleen and neck glands by 75 per cent. Several thoracenteses were performed, yielding bloody fluid. He had had, during these past few weeks, temperature ranging from normal to as high as 100.4°. The X-ray treatment given had totalled 960 roentgen units over the spleen, anteriorly and laterally, 500 roentgen units over right and left cervical areas, 800 roentgen units over the anterior and posterior chest directed at the mediastinum, and 800 roentgen units over each inguinal region. Before X-ray treatment his blood studies had shown hemoglobin 80 per cent, red blood

cells 3,658,000, white blood cells 7,860. Differential: polymorphonuclear neutrophiles 82 per cent, basophiles 1 per cent, eosinophiles 1 per cent, small lymphocytes 15 per cent, monocytes 1 per cent. Average red blood cell diameter 7.84.

Physical examination: The patient showed evidences of recent weight loss, a brassy cough, dyspnea, and orthopnea. There was mild pallor. There was moderate generalized enlargement of the superficial lymph nodes, and the glands were firm, discrete, and insensitive. There was bilateral hydrothorax, and the fluid removed therefrom on several occasions was a serosanguineous transudate. The liver edge extended four finger-breadths below the costal margin, and the firm spleen edge almost to the umbilicus. There was slight pitting edema of the ankles. The chest X-ray plate confirmed the presence of fluid.

Laboratory examinations: The Wassermann reaction was negative. Nonprotein nitrogen and blood sugar were normal, as were stool and urine studies. Red blood cells 4,120,000, hemoglobin 12.4 gm. per 100 cc., volume of packed red blood cells 37.0, corrected sedimentation rate 10 mm. in 60 minutes, white blood cells 1,000–2,900 with 10 polymorphonuclear neutrophiles and 20 small lymphocytes of 30 cells counted, platelets 71,000. The basal metabolic rate was +4 per cent. Serum protein 5.52 gm. per 100 cc. Albumen/globulin ratio 67/33.

The lymph gland removed before X-ray treatment showed the characteristic follicular hyperplasia described in Case 2.

Comment: Five cases of follicular lymphoblastoma have been presented. All were in white males on the private medical service, aged respectively 39, 30, 50, 42 and 29 years. All had fairly general superficial lymphadenopathy, some pronounced in degree. At least two had large masses of mesenteric nodes. The spleen was palpable in all cases: in three it reached to or beyond the level of the umbilicus; in two it was just palpable. The known duration of illness was respectively 13 months, 18 months, 4 years, 10 months, 9 weeks; the last two patients were still alive and well, the first three had succumbed in the times noted. All had normal or low total white cell counts, usually dropping considerably after X-ray therapy. Three patients had essentially normal erythropoiesis as judged by blood counts; one, in spite of a normal bone marrow, developed an anemia that responded well to transfusion and liver therapy; one had an intractable anemia. Anemia when present was normocytic in type. Fever was absent in two, terminal in two, slight in one who still survives. The differential white counts showed nothing remarkable except the atypical monocytic cells noted in Case 2 and the few terminal myelocytes noted in Case 1. The original differential counts in Case 5 were normal; after

X-ray therapy the counts were unsatisfactory because of leukopenia. Basal metabolism was elevated in two of the three cases so tested (higher than may be accounted for by the fever present in one of these), normal in one. Uric acid was much elevated in the two cases tested, though both of these had elevated nonprotein nitrogen as well. One patient had recurrent chylous pleural effusion; one recurrent serosanguineous pleural effusion. One patient had terminal jaundice and gastric hemorrhage. One case was complicated by hypertensive cardiovascular disease.

A correlation of the course of illness and response to X-ray with degree of invasiveness and destruction of follicular arrangement as seen microscopically would be of definite value for prognosis. The material herein presented is only fairly satisfactory in this respect. Two of the cases showed the changes limited strictly to the follicles and might have been classified microscopically as benign; one was clinically fairly benign, the other ran a rapid and malignant course. Three of the cases showed invasion of the pulp by germinal center cells and thus appeared more malignant microscopically; of these, two ran malignant clinical courses. The other still survives and achieved a good result from X-ray treatment.

On final analysis, these cases have seemed less benign than the majority of cases hitherto reported. This, however, is the only manner in which they differ from "classical" cases. They represent instances of the variable course this disease may run. It should be pointed out that the malignant type of clinical course has no certain pathologic counterpart; and on the other hand it is to be noted that Symmer's seven cases reported as "transformation of follicular lymphoblastoma to polymorphous cell sarcoma of the lymph follicles" show none of the clinical characteristics of a more malignant disease.

Group II

Four additional cases of lymphoblastoma in the records of The Johns Hopkins Hospital have been particularly interesting both as to clinical and pathological grouping. Clinically they rather closely resemble the group of follicular lymphoblastoma, except in length of life; microscopically they present a different and more malignant picture.

Case 1a. (Unit 48905.) A white woman, aged 60, was first seen at the Johns Hopkins Hospital on February 11, 1923 on the service of Dr. T. B. Futcher, complaining of pain in the abdomen and right hip of six weeks' duration. Eighteen months before, because of a variety of abdominal complaints, Dr. Bloodgood had explored the abdomen and found a huge gall-bladder from which two liters of bile were removed. Since this operation the patient had felt weak and below par. Six to seven weeks before entering the hospital there appeared pain in the right upper quadrant of the abdomen and in the right hip and shoulder, the abdominal pain being in the nature of a girdle pain and worse while standing. Two weeks before entrance she first noted tender swollen right inguinal glands. There had been a 35 pound weight loss in the preceding 18 months.

Physical examination revealed the patient to be pale and underweight. The head and neck were normal. The percussion note was slightly impaired and the voice sounds increased over the left lower lung field. The area of heart dulness measured 2.5 x 14 cm. There was a loud apical first sound and a short presystolic rumble. The spleen was not felt. There was slight enlargement of both right and left inguinal glands. Large firm nodules were felt in the epigastrium and the right hypochondrium, not connected with the liver. In the right side of the abdomen was a nodular, irregular mass about 8 x 10 cm. in diameter.

Laboratory examinations: Hemoglobin 65 per cent, red blood cells 3,420,000, white blood cells 9,200. Differential: polymorphonuclear neutrophiles 80.5 per cent, basophiles 1.0 per cent, small mononuclears 8.5 per cent, large mononuclears and transitionals 10 per cent. The Wassermann reaction was negative. X-ray pictures of the spine showed only osteoarthritis. Barium enema was negative. In the gastro-intestinal series it was noted that the outline of the duodenum suggested that it coursed around a mass.

Fever rose daily from 98° to 102°. She left the hospital and died at home on March 7, 1923. Autopsy was performed at the Johns Hopkins Hospital on March 7, 1923. Dr. William G. MacCallum's notes on the points at issue were as follows: "There is a most extraordinary combination of large tumor with lobular masses clustered about the retroperitoneal blood vessels and extending into the mesentery, with secondary growths in the spleen, liver, lung, diaphragm, kidney and vertebrae. These nodules look at first sight like Hodgkin's disease in their distribution in the spleen and raise that suggestion, but on closer inspection they do not look exactly like Hodgkin's disease even in the spleen because they are perfectly sharply outlined, yellowish, rather translucent masses and the distribution in all the other organs is quite unlike that of Hodgkin's disease, especially the distribution of very numerous minute nodules about 2 mm. in diameter throughout the kidneys and in the scattered lenticular nodules all over the under-surface of the diaphragm. The tumor is practically the same throughout and appears to be composed of rather large cells with vesicular nuclei and some larger ones which have multiple nuclei. It has a delicate reticulum and in the lymph glands it seems to invade along channels such as lymph sinuses. In the spleen it appears to occupy the Malpighian bodies distending them into thin rings of lymphoid

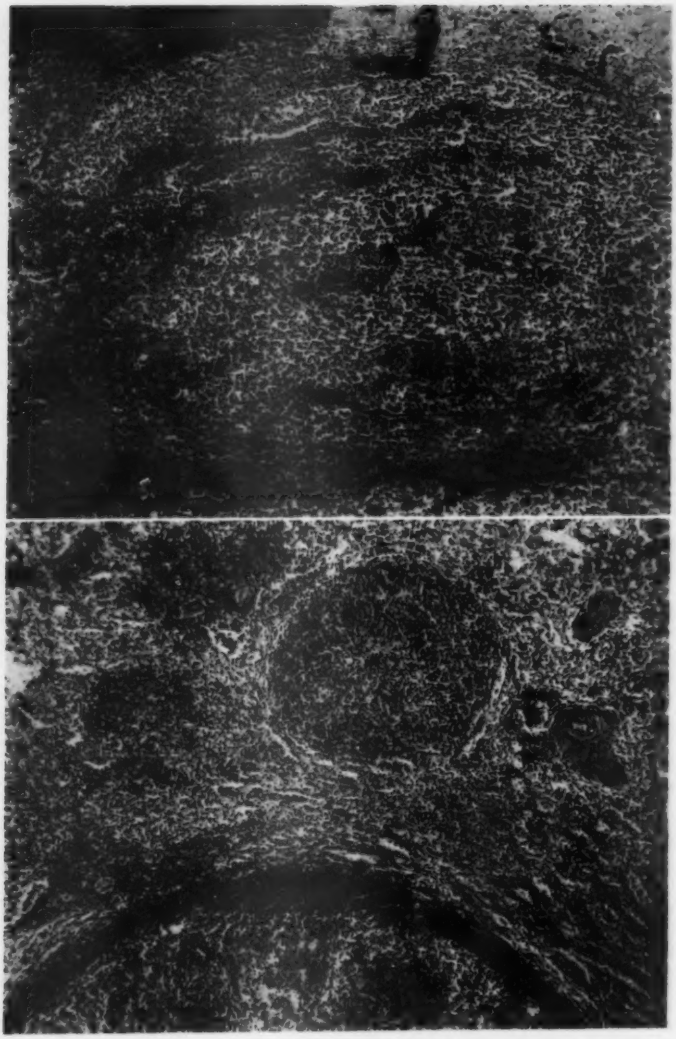

FIG. 2. (CASE 1A). SECTIONS OF TISSUE OBTAINED AT AUTOPSY. ×60

Above, lymph node, showing widespread involvement by tumor cells with only a suggestion of follicular structure.

Below, spleen, showing tumor cells mostly confined to greatly enlarged Malpighian bodies.

cells. In the liver and kidney it appears in pure form as also in the lung, diaphragm, etc. It does not seem to correspond with the structure nor the distribution of lymphosarcoma. It is not homogeneous enough and has not the arrangement of cells in the lymphosarcomas commonly found in the abdominal organs."

The portions of Dr. F. B. Kindell's notes bearing on the tumor record the following information: "The spleen weighs 280 gm. and measures 13 x 8 x 5.5 cm. On section the spleen is shot full of white, irregularly rounded tumor masses as large as 1 cm. in diameter, and the Malpighian bodies are readily visible. Similar nodules are found through most of the other organs. Microscopic examination of the nodules in the spleen shows them to resemble enormously enlarged Malpighian bodies with pale centers and thin rims of lymphocytes. The central areas are composed of the same tumor cells seen elsewhere, and there are many hyaline necrotic areas. In the spleen pulp are great numbers of phagocytic cells containing red blood cells and pigment. All the lymph glands sectioned show the same picture. There are areas which have the general appearance of germinal centers, often with necrotic or hyaline pink staining material in the center and small lymphocytic cells at the periphery. The large central cells are indistinguishable from those in areas of undoubted tumor. The capsules of the glands are often destroyed, the tumor extending into the surrounding connective tissue and fat. Here again can be seen clumps of lymphoid cells closely associated with the tumor cells. The tumor cells are round, or slightly oval, with scanty cytoplasm staining rather dark bluish-pink with eosin and hemotoxylin. The nuclei are rather densely staining vesicular and contain one or two large nucleoli. There are fairly numerous mitotic figures. The cells vary in size and there are many large multinucleated cells with from two to ten nuclei closely bunched in the center of the cell, overlapping and often forming a rosette. There are regularly placed necroses in the larger tumor masses. The numerous instances in which clumps of tumor cells appear in small veins is very striking." There was scarring of the mitral valve.

Case 2a. (Unit 18584.) A white man aged 42 entered the Johns Hopkins Hospital on the service of Dr. L. F. Barker on May 23, 1928, complaining of weakness. This symptom had been increasingly severe since its onset five months before. There had been some exertional dyspnea. His spleen had been found to be enlarged in January 1928. The past history was negative save that he was seen by Dr. W. S. Thayer in July 1911 following a Stokes-Adams syncopal attack and since that time his pulse rate had been 42–44 per minute. He had had three boils in the two weeks preceding entrance.

Physical examination: The patient was 17 to 18 pounds under his usual weight. Skin was lemon-yellowish. There were the discharging sinuses of furuncles on the left chest and in the left axilla. There were pea-sized, discrete, firm, insensitive cervical, axillary, inguinal, and right epitrochlear lymph nodes. The heart was a little enlarged to the left. Blood pressure was 120/58. The pulsations of the jugular veins were more rapid than those of the radial arteries, without any establishable numerical relationship. The arterial pulse rate was 40 and regular.

There was a rough systolic bruit heard all over the precordium, transmitted to the axilla and neck. There was pitting edema over the sacrum and shins. The lung bases were high, and the left lung was dull below the angle of the scapula, and the right from three finger-breadths below the angle of the scapula. Vocal fremitus was increased below the fifth thoracic spine. The firm spleen edge extended to two finger-breadths above the umbilicus.

Laboratory examinations: The electrocardiogram showed complete heart block. Red blood cells numbered 2,957,000. Hemoglobin 50 per cent. White blood cells 14,800. Differential: polymorphonuclear neutrophiles 72.8 per cent, eosinophiles 0.8 per cent, basophiles 1.2 per cent, small mononuclears 20 per cent, transitionals 5.2 per cent. There was definite anisocytosis, poikilocytosis, and basophilia. Two normoblasts were seen; the platelets appeared normal. There were a few unidentified young white cells in the smear. The Wassermann reaction was negative. The gastric analysis showed 10° free hydrochloric acid, 15° combined. Urine showed moderate amounts of albumen, an occasional cast, many red cells, and a few white cells. X-ray examination of the chest was negative except for an enlarged heart. Blood nonprotein nitrogen was 43 mg. per 100 cc., uric acid 6.2 mg. per 100 cc., fasting blood sugar 97 mg. per 100 cc. Icterus index was 20.5. Gastro-intestinal X-rays showed the stomach pushed to the right. X-rays of the bones were negative. Blood culture was sterile.

The spleen gradually increased in size, and the icterus remained stationary. There was a terminal spiking fever. The patient died suddenly on May 30, 1938.

Autopsy was performed on May 30, 1938, by Dr. Squier. The retroperitoneal and cervical nodes and the spleen were greatly enlarged and the axillary, peribronchial and peritracheal nodes shared in the process. The spleen weighed 2890 gm.

Nodules of tumor were seen to replace normal lymph gland structure all through the body, and there were nodules in the vertebrae as well. In the liver were both discrete nodules and portal infiltration by tumor cells. The cells of the tumor seemed to be more polymorphous than in the usual lymphosarcoma. There were many localized areas of necrosis and fibrosis, and also some multinuclear cells. It was not thought, however, that this tissue represented Hodgkin's disease. Cells like those seen elsewhere made up the nodules in the spleen, and here the tumor masses were seen to take the place of the Malpighian bodies; delimitation by rinds of adult lymphocytes was present but neither frequent nor complete. The tumor cells invaded the walls of veins and the trabeculae of the spleen, and the capsules of the lymph nodes.

Case 3a. (Unit 38287.) A colored man aged 50 entered the Johns Hopkins Hospital on July 25, 1931 complaining of a swollen neck and forty-five pound weight loss in the past two months. In February 1931 he had first noted a lump in the right side of the neck and by April this had grown to the size of an egg. He was seen in the Johns Hopkins Hospital dispensary where a mass of matted glands was noted in the right side of neck, extending about the ear and including the submaxillaries; enlarged sublinguals and glands in the left cervical triangle

were also noted. He was given twelve Alpine lamp treatments. At about the time this treatment was started there appeared rapid enlargement of the axillary and inguinal lymph glands, and a mass in the right upper quadrant of the abdomen.

Physical examination: The patient was emaciated. There was general glandular enlargement with a large matted mass in the right side of the neck the size of a grape-fruit, acorn-sized glands in the left side of the neck, walnut-sized glands in the axillae and groins, and small pea-sized glands over various bony prominences. These glands were firm and insensitive. The tonsils were large, red and cryptic. The area of heart dulness was a little enlarged, measuring 11 cm. to the left. The blood pressure was 152/120. The abdomen contained a large mass in the right upper quadrant reaching from the costal margin to the iliac crest in the axillary line, to the umbilicus in the mid-line, to the costal margin in the left mid-clavicular line; the edge of this mass, which was thought to be liver, was rounded and a little tender. The spleen was not felt. The eyes were prominent. The left optic disc was hazy with glistening streaks radiating from it, and there was one small hemorrhage in the left fundus.

Laboratory examinations: Red blood cells 3,400,000, hemoglobin 75 per cent, white blood cells 8,600. Differential: polymorphonuclear neutrophiles 73 per cent, small lymphocytes 10 per cent, large lymphocytes 1 per cent, eosinophiles 1 per cent, monocytes 15 per cent. Blood nonprotein nitrogen 44 mg. per 100 cc. Van den Bergh test showed a delayed biphasic reaction: 1.4 mg. bilirubin per 100 cc. The Wassermann reaction was negative. The urine was normal. The chest plate was negative. The bones were negative on X-ray examination except for a small area of absorption in the right ulna. Temperature varied from 100° to 103°, with terminal 108°. He died suddenly on July 31, 1931. Autopsy was performed on August 1, 1931 by Dr. Fite. The spleen was enlarged and weighed 300 gm., and throughout its pulp were scattered numerous indistinct grey nodules. The liver was greatly enlarged, weighing 4,300 gm., and contained numerous large and small masses. The tumor also involved the lymph glands at the base of the mesentery, about the pancreas, the right side of the neck and axillary and mesenteric nodes as well. On microscopical examination the tumor nodules everywhere were seen to consist of great masses of cells with very little stroma. The cells were fairly uniform in type and looked like large immature cells of the lymphocyte series. In the liver there were discrete nodules as well as periportal infiltration. The spleen showed a truly remarkable picture. The tumor cells were found only in the Malpighian bodies, enlarging and distorting them greatly, and in many cases spreading beyond the confines of these bodies; the pulp, in general, and the sinuses were not invaded.

There was, in addition, a myxoma of the left optic nerve sheath.

Case 4a. (Unit 148469.) A white man aged 45 entered the Johns Hopkins Hospital on August 26, 1938, on the service of Dr. H. M. Thomas, Jr., complaining of abdominal pain. In February of 1938 he had first noted "drawing" pain in the left flank when lying down, which was relieved by extending the thigh; there was some radiation into the lower abdomen and to the other side, of the nature of a

girdle sensation. He noticed that he became easily fatigued. X-ray pictures taken at this time were said to have shown a shadow in the region of the left kidney. He was well during May. During June ease of fatigue reappeared, and in July and August the pain in the left side began once more. In August 1938 slight afternoon fever was discovered. Late in August he developed sharp pain in the right flank radiating through to the loin and into the right lower quadrant, relieved by lying on the right side.

Physical examination: There were marked dental caries and gingivitis. There was one enlarged left epitrochlear and one left axillary lymph node. The diaphragm seemed high. The heart was transversely placed. Liver dulness extended from the fourth rib to two finger-breadths below the costal margin. The spleen was just barely palpable. The left kidney was palpable.

Laboratory examinations: Red blood cells 4,330,000, hemoglobin 12.3 gm. per 100 cc., white blood cells 3,700, volume of packed red cells 37 per cent, corrected sedimentation rate 32 mm. in one hour, mean corpuscular volume 86, mean corpuscular hemoglobin 29, corpuscular concentration of hemoglobin 33. Differential: juvenile neutrophiles 5 per cent, segmented neutrophiles 36 per cent, eosinophiles 12 per cent, small lymphocytes 24 per cent, monocytes 23 per cent. Uric acid 8.7 mg. per cent. The basal metabolic rate was +28 per cent. The heterophile antibody test was positive in 1:4 dilution. Agglutinations for typhoid and melitensis were negative. X-rays of gastro-intestinal tract, bones, and abdomen were negative. Intravenous pyelograms showed rotation of both kidneys. Biopsy of a left axillary lymph gland was performed on August 29, 1938, and variously reported as follicular lymphoblastoma, reticulum-cell sarcoma, lymphosarcoma, and macrophage-cell sarcoma. Biopsy of the sternum on August 29, 1938, revealed normal bone marrow. He was given 450 roentgen units of deep X-ray to the lower abdomen.

Anemia appeared and was progressive; there was some enlargement of the cervical lymph nodes; great masses of glands appeared in the epigastrium and left lower quadrant of the abdomen, and there was rapid enlargement of the spleen which reached, by the time of death, on September 24, 1938 five finger-breadths below the costal margin.

Dr. M. M. Wintrobe examined the blood smears. The differential cell counts were: (*September 6*) juvenile neutrophiles 12 per cent, segmented neutrophiles 47 per cent, eosinophiles 1 per cent, basophiles 1 per cent, small lymphocytes 9 per cent, monocytes 23 per cent, young monocytes and macrophages 7 per cent; (*September 9*) juvenile neutrophiles 12 per cent, segmented neutrophiles 49 per cent, eosinophiles 3 per cent, basophiles 1 per cent, small lymphocytes 18 per cent, monocytes 15 per cent, large monocytes 2 per cent. Dr. Wintrobe's comment on the smears was as follows: "a number of the monocytes, particularly in the smear of September 6, are very unusual types of cells. Some are unusually big. The nuclei show the characteristic structure of a monocyte. In the big ones the cytoplasm is abundant and often contains vacuoles. Then again, cells with this similar nucleus are seen in which the cytoplasm is deep blue and shows few granules and no vacuoles. These cells may be young monocytes."

Autopsy was performed on September 24, 1938, by Dr. D. Woodruff. There was found to be a huge mass of tumor, involving lymph glands in the retroperitoneal tissue from the pelvis to the diaphragm, measuring 40 x 20 x 10 cm., displacing and rotating both the kidneys. The mass of mediastinal lymph nodes measured 10 x 4 x 4 cm. On section these masses appeared as hard white tumor tissue. The spleen weighed 1800 gm., and measured 28 x 20 x 10 cm.; the pulp was everted on the cut surface, was uniform dark reddish-purple, and over this surface were scattered many small yellowish areas about 1 mm. in diameter. Section through the lymph nodes in the mass of retroperitoneal glands showed a uniform whitish structure with some hemorrhage and necrosis. There was some involvement of the mesenteric nodes and of those along the lesser curvature of the stomach.

Dr. Arnold Rich's notes on the microscopic sections are as follows: "Sections from the retroperitoneal tumor mass show that it is composed of cells of varying size and shape, but they are for the most part rather large cells. The nuclei are round, oval or somewhat irregular in outline; they contain a moderate amount of chromatin but are not decidedly hyperchromatic. There are one or more nucleoli. The cytoplasm varies in amount and in contour. There is very little stroma; this is represented by delicate fibrils and capillaries which ramify between groups of the cells. Each of the tumor cells is separate from the others, and nowhere do they form a continuous tissue. The lymph nodes are filled up uniformly with these same cells, so that in most cases the entire architecture of the node is obliterated. In places the cells extend from the node into the surrounding tissue. In the spleen the Malpighian bodies are converted almost entirely into cells of the same sort, and these extend out to invade the pulp. In the main tumor mass and in the spleen and lymph nodes there are numerous mitoses in the tumor cells. Neither in the main tumor mass nor in the lymph nodes is there any follicular arrangement such as that seen in follicular lymphoblastoma. In the spleen, whereas the tumor cells are most concentrated in the Malpighian bodies, these are not very greatly enlarged nor is there any follicular arrangement here in the sense that a central mass of large cells would be surrounded by a zone of smaller lymphocytes. The situation is rather that the sites of the Malpighian bodies are now represented by an accumulation of the tumor cells to the almost complete exclusion of the normal lymphoid elements.

"In the periportal spaces of the liver there are small accumulations of mononuclear cells. Some of these are plasma cells, others small lymphocytes, some possibly mononuclear phagocytes, and there may also be among these cells some of the tumor cells. These infiltrations are not marked, and rarely if ever enlarge the periportal area. No accumulations of the tumor cells are found replacing the cells in the sections of marrow. The tumor cells wherever found in other situations have the same character and arrangement as described above.

"What the precise nature of these cells may be may be subject to individual interpretation. There does, however, seem to be persuasive evidence that they represent lymphoblasts, or at least that we have to do with a tumor of lymphocytic origin. One of the persuasive points is the fact that in the spleen it is the Mal-

pighian bodies which are decidedly more involved than the pulp. Malpighian bodies are found completely converted into the tumor cells, with adjacent pulp showing only a sparse scattering of these cells. Under very low magnification these tumor-filled Malpighian bodies stand out sharply against the much less involved pulp. If this were a tumor arising from the mononuclear ("reticulo-endothelial") phagocytes, one would expect to find the pulp more prominently involved than the Malpighian bodies, for it is in the pulp that the mononuclear phagocytes normally lie in the greatest abundance. Another point in favor of the lymphocytic origin is the fact that the Wright stains of smears of the tumor cells

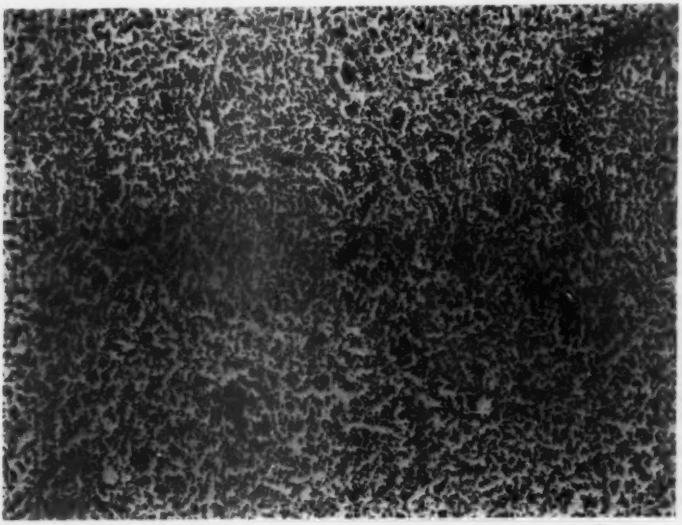

FIG. 3. (CASE 4A). LYMPH NODE SHOWING DIFFUSE INVOLVEMENT WITH LOSS OF FOLLICULAR STRUCTURE. ×60

made from the tissues at autopsy show cells which are quite like lymphoblasts. Uniformly their cytoplasm stains clear blue and is without granulations. In this they differ completely from the frank monocytes that were found in the blood smears during life. Finally the tumor cells, while involving the spleen and the lymph nodes all over the body, are not found in nodules in the bone marrow. Their proliferation, except where they extend directly into surrounding tissues, is confined to lymphoid tissue, although the bone marrow, of course, is richly supplied with mononuclear ("reticulo-endothelial") phagocytes.

"None of the above points is perfectly conclusive, but they seem to weigh against the view that the tumor cells represent a proliferation of the mononuclear phagocytic cells."

Comment: Four cases of lymphoblastoma have been presented above. They occurred, respectively, in a white woman aged 60, a white man aged 42, a colored man aged 50, a white man aged 45. The known duration of illness was one month, five months, four months, and six months, respectively. Fairly obscure and apparently indolent at first, the disease became highly malignant terminally. Two patients showed general superficial lymphadenomegaly which in one was fairly symmetrical, while in the other there was a great mass in the neck. In two patients the lymphadenomegaly was primarily and preponderantly abdominal. All had enlarged spleens, two of which were felt during life. In these last two cases, recognizable and rapid enlargement of the spleen took place shortly before death. One of the palpably enlarged spleens was associated with generalized superficial lymphadenomegaly, one with huge masses of abdominal glands. All of the patients had fever of intermittent character during the observed terminal phases. One had a leukopenia, one a mild leukocytosis, two normal white counts. None showed any notable change in differential white counts except case 3a, which showed a monocytosis, and case 4a, which showed a monocytosis as well as the few young monocytes or macrophages described. All had terminal normocytic anemia of moderate degree. Bone marrow in the one case examined antemortem was normal, as were all the necropsy specimens of marrow. The blood uric acid in the two cases in which it was estimated (Cases 2a and 4a) was high, and in neither was the nonprotein nitrogen elevated.[1] One patient was treated with X-ray and failed utterly to respond; the time was too short and the dosage (450 roentgen units) too small to justify any conclusions as to the possible efficacy of X-ray treatment in this particular variety of lymphoblastoma.

These four cases, then, appear to represent peculiar, malignant forms of lymphoblastoma or lymphosarcoma. They differ clinically from the usual lymphosarcoma in the constancy with which the spleen is involved. Pathologically they present a fairly characteristic picture; in one respect the pathological findings resemble follicular lymphoblastoma, namely the uniformity with which the splenic

[1] We have noted high blood uric acid values in lymphoblastomata other than leukemia in which they are well known. In one case of Hodgkin's disease figures consistently above 9 mgm. per cent were encountered.

involvement is confined to or most pronounced in the Malpighian bodies; and, in truth, the microscopical picture in the spleen in one of them (Case 1a) shows areas indistinguishable from those found in cases of follicular lymphoblastoma wherein the germinal center cells have slightly involved the pulp. In one instance (Case 1a) a similar picture was occasionally seen in the affected lymph nodes. In Cases 2a 3a, and 4a, however, the picture in the lymph nodes was that of a lymphosarcoma, although in Case 4a many interpretations, as to the particular type of lymphosarcoma it represented, were rendered after a study of the lymph node obtained for biopsy. In none of the cases was the involvement of the spleen similar to that described in the rare lymphosarcomatoses wherein irregular nodules of tumor tissue may be found in the spleen.

There is a definite similarity between Case 1a and the case reported by Symmers as "necrotic folliculitis of the lymph nodes and spleen," and included by him as one of the late changes that may be seen in follicular lymphoblastoma.

CONCLUSIONS

In the description of the five cases of follicular lymphoblastoma in the first group of cases described in this paper we have presented further evidence for considering this group as a distinct clinical-pathological disease entity. Examination of the protocols of the relatively few cases of follicular lymphoblastoma that have been reported previously leaves little doubt that most of them represent a comparatively benign form of lymphatic tumor which is peculiarly radio-sensitive. The more malignant and rapid course of several of the cases reported here is worthy of special note; in this regard only do they differ from the usual. Pathological study appears to indicate that in either the benign or the more malignant form the tumor cells may invade neighboring tissues and not be wholly confined to the germinal centers of the lymph follicles. No apparent relationship has been found between the clinical course and the invasiveness of the tumor cells as seen in microscopic sections.

The four cases which comprise the second group represent instances of malignant lymphoblastoma, and each one very likely represents a stage somewhere intermediate between follicular lymphoblastoma and

lymphoblastic sarcoma. As more and more cases are carefully studied it appears that almost every shade of variation of these pictures is possible.

The typical case of benign follicular lymphoblastoma with splenomegaly is capable of fairly confident clinical recognition, but the diagnosis requires pathological corroboration, for without the examination of an excised lymph node, the picture may lead one to suspect an unusual Hodgkin's disease. The more malignant, rapidly progressive cases, exemplified by the four autopsied cases, present a more difficult problem of clinical classification; the blood and bone marrow pictures serve to differentiate them from leukemia, the gland biopsy from Hodgkin's disease which they otherwise resemble very closely; and the gross splenomegaly at least suggests the correct diagnosis even though the biopsy may not serve to differentiate it from the usual lymphosarcoma. The serious attempt to make this differentiation during life is certainly of great importance, both for prognosis and therapeusis. A case of rapidly progressive lymphoblastoma with splenomegaly, proven not to be aleukemic lymphatic leukemia, and differentiated from follicular lymphoblastoma and Hodgkin's disease by the microscopic structure of an excised lymph gland, falls either into the extremely rare category of lymphosarcomatosis with large splenic metastases or into the above-described subdivision of highly malignant lymphoblastoma.

SUMMARY

1. Five cases of follicular lymphoblastoma are reported. In this series follicular lymphoblastoma has not proved to be entirely benign despite the usual dramatic early response to radiotherapy. The length of response to irradiation can not be prophesied by the presence or absence of microscopic evidence of invasiveness.

2. The possibility of clinical recognition of follicular lymphoblastoma is emphasized.

3. Four cases are described which represent malignant lymphoblastomata of an unusual but characteristic type. They present the following features: general or local lymphadenomegaly; splenomegaly due to the presence of tumor cells which are localized especially in the Malpighian bodies; lymph nodes showing diffuse infiltration with

lymphoblastic cells; normal blood picture save for moderate anemia; a rapidly fatal course.

Dr. Arnold Rich has been kind enough to supervise the collection of pathological material for this report.

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TREATMENT OF ADDISON'S DISEASE WITH PELLETS OF CRYSTALLINE ADRENAL CORTICAL HORMONE (SYNTHETIC DESOXY-CORTICOSTERONE ACETATE) IMPLANTED SUBCUTANEOUSLY[1]

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Deanesly and Parkes (1) reported that in experimental animals the subcutaneous implantation of tablets of crystalline estrogens and androgens provided an efficient and convenient method of administering sex hormones. In a previous report we observed that bilaterally adrenalectomized dogs could be maintained in excellent condition by implanting, subcutaneously, pellets of crystalline desoxy-cortiocosterone acetate (2). The hard consistency of the pellets and the slight water solubility of the compound resulted in a slow rate of absorption and hence prolonged action. It was possible to remove, weigh and reinsert the pellets at frequent intervals. The rate of absorption could be determined from the change in weight since the pellets were composed only of crystals of hormone. Pellets weighing 50–150 mg. were absorbed at a rate of from 0.25 to 0.40 mg. per day. This rate of absorption did not vary significantly in different animals, and did not seem to be related to the animal's condition or hormone requirement. In these studies the number and the size of pellets necessary for maintenance were compared with the daily requirement of desoxy-corticosterone acetate in oil, injected subcutaneously. It was noted that a considerable saving in hormone (25–30 per cent) was effected by pellet implantation. Furthermore, the number of pellets required for maintenance could be predicted rather accurately

[1] This study was aided in part by a grant from the Committee on Research in Endocrinology, National Research Council.

from the daily requirement of hormone in oil. The advantages which resulted from the implantation of pellets of synthetic adrenal cortical hormone in dogs prompted the investigation of the use of this method of treatment for patients with Addison's disease.

In the present report, six patients with Addison's disease were selected for treatment with pellet implants. None of these patients could be maintained in good condition by means of sodium chloride therapy alone (see protocols). Since the supply of crystalline synthetic hormone available for this study was limited, added sodium chloride therapy was given to five of the six patients as it has been shown (3) that added sodium chloride (8–12 gm. daily) greatly reduces the requirement of desoxy-corticosterone acetate. The adequacy of treatment with desoxy-corticosterone acetate alone in maintaining bilaterally adrenalectomized dogs in good condition despite a diet low in sodium chloride content, and in maintaining patients with Addison's in good condition without supplementary sodium chloride treatment has been demonstrated (2, 3).

METHODS

Six patients with Addison's disease were selected for study. The patients were provided with a diet of constant mineral intake. The care of the patients, and the methods used in the analysis of the diet, blood and urine specimens have been described (3).

The daily maintenance dose of desoxy-corticosterone acetate[2] in sesame oil, injected once daily, was determined. The maintenance of (*a*) optimum body weight (*b*) normal blood pressure (*c*) normal plasma volume, (*d*) positive sodium and chloride balance and (*e*) normal concentration of plasma electrolytes, were considered as evidence of adequate treatment. Daily injections of the hormone in oil were then discontinued, and, under local anesthesia, pellets of crystalline desoxy-corticosterone acetate, weighing 50–150 mg. each, were inserted subcutaneously in the infrascapular region. The implantation of pellets occasioned no untoward reaction.

[2] The desoxy-corticosterone acetate used in this study was supplied by Messrs. Ciba through the courtesy of Doctors K. Miescher and E. Oppenheimer. Desoxy-corticosterone acetate (*Percorten*) is not yet available commercially.

PREPARATION OF THE PELLETS

Under sterile conditions, pellets weighing 50–150 mg. were prepared by pounding a suitable quantity of crystalline desoxy-corticosterone acetate in a specially constructed mold (2). Sterilization may be effected by dissolving the crystals in hot acetone, filtering the solution through a Seitz filter, and then evaporating the solution to dryness. No binding substance was employed. The pellets measured 6.5 mm.

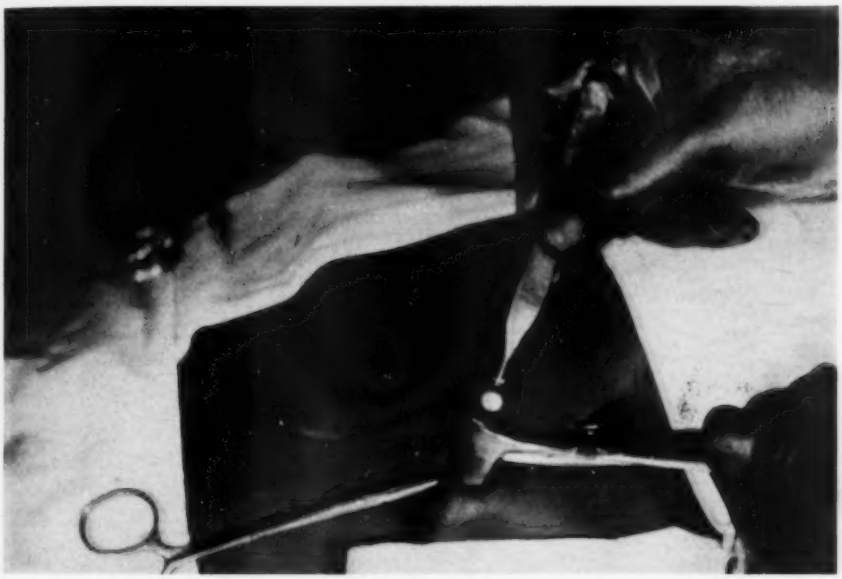

FIG. 1. IMPLANTATION OF PELLET OF DESOXY-CORTICOSTERONE ACETATE

in diameter by 2–6 mm. in thickness. The surface area of pellets of this size varied from 107.2 sq. mm. (2.0 mm. in thickness) to 188.9 sq. mm. (6.0 mm. in thickness). Silk thread or silver wire was attached to the pellets to facilitate localization at a later date. The decrease in the weight of the pellets measured the amount of hormone absorbed. The hardness of the pellets and the relative insolubility of desoxy-corticosterone acetate in water delayed disintegration and resulted in slow, prolonged absorption.

OBSERVATIONS

Patient M. M., (see protocol), was admitted to the hospital in poor condition, despite the daily ingestion of 15–20 gm. of sodium chloride. On admission her weight was found to be 51.3 kg., blood pressure 88/64 mm. Hg, plasma concentration of sodium 131.4 m.eq., of chloride 96.2 m.eq. and of potassium 5.9 m.eq. per liter, blood non-protein nitrogen 24 mg. per 100 cc. and blood sugar (fasting) 69 mg. per 100 cc. At this time, under local anesthesia, two pellets of desoxy-corticosterone acetate (75 and 105 mg. respectively) were implanted in the infrascapular regions, the added sodium chloride therapy (12 gm.

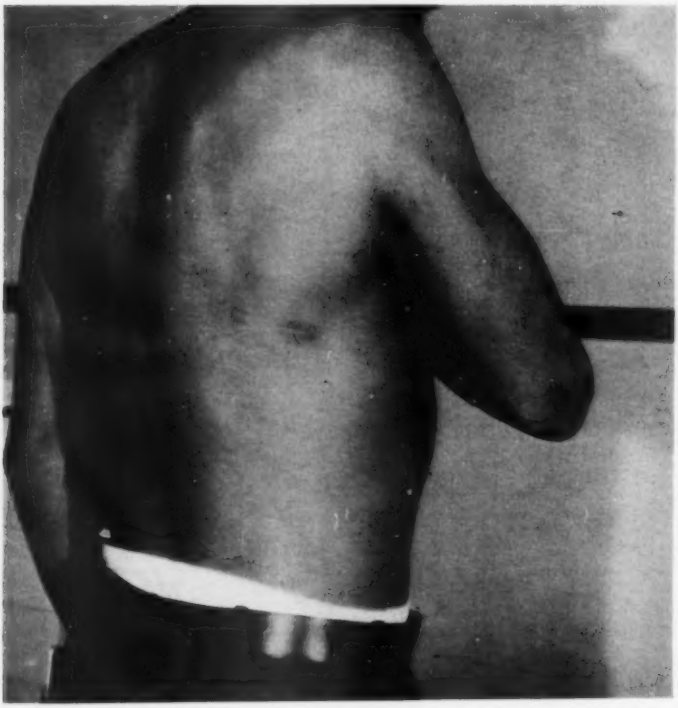

FIG. 2. THE SITE OF OPERATION FIVE WEEKS AFTER IMPLANTATION OF PELLETS OF DESOXY-CORTICOSTERONE ACETATE (PATIENT D. B.)

daily) being continued. During the first week following the implantation of the pellets the patient gained 1.8 kg. Hemodilution was observed, the hematocrit decreasing from 43.2 per cent to 34.8 per cent cells. The plasma concentration of sodium increased from 131.4 m.eq. to 137.8 m.eq. per liter. The plasma concentration of chloride increased from 96.2 m.eq. to 100.2 m.eq. and plasma potassium decreased from 5.9 m.eq. to 4.3 m.eq. per liter. At this time two additional pellets, weighing 65 mg. each, were inserted in an effort to increase the patient's blood pressure which during this period had shown no significant improvement. Two months after the pellets were inserted, the patient's blood pressure was 96/60 mm. Hg, and she was performing all of her household duties for the first time in more than 2 years. Three months after the pellets were implanted, she had gained 4 kg. in weight and her blood pressure was found to be 110/80 mm. Hg. At this time the plasma volume and plasma concentration of electrolytes were normal.

One hundred and ten days after implantation, two of the pellets were removed, weighed, reinserted and, an additional pellet weighing 53.2 mg. was inserted at this time. It was noted that during the period of 110 days one pellet had decreased from 105.0 mg. to 74.2 mg., a loss of 30.8 mg. The second pellet had decreased from 75.0 mg. to 43.7 mg., a loss of 31.3 mg. (chart 1). Thus the pellets had been absorbed at a rate of 0.28 mg. and 0.29 mg., respectively, daily. This rate of absorption corresponded very closely to that observed in the experiments on adrenalectomized dogs (chart 1). If it may be assumed that the two remaining pellets were absorbed at the same rate as those which had been weighed, then a total of 1.2 mg. of hormone were supplied daily by the four pellets. The addition of the fifth pellet on the 110th day increased this total to approximately 1.5 mg. daily. Five months after the original implantation of pellets this patient weighed 54.7 kg., a gain of 3.4 kg. and her blood pressure had increased from 88/64 to 112/72 mm. Hg. The plasma volume at this time was found to be 2660 cc. (95% of normal) and the plasma concentration of sodium 140.4 m.eq. and of chloride 105.6 m.eq. per liter. The blood non-protein nitrogen was 26 mg. per 100 cc. and the blood sugar (fasting) 68 mg. per 100 cc. At this time the patient appeared to be

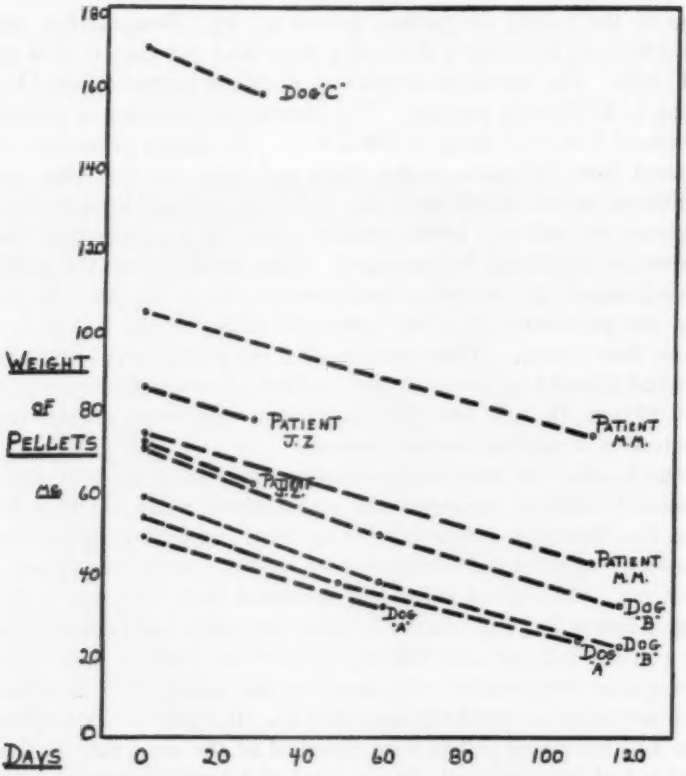

CHART 1. THE RATE OF ABSORPTION OF PELLETS OF SYNTHETIC HORMONE IMPLANTED SUBCUTANEOUSLY IN ADRENALECTOMIZED DOGS AND IN PATIENTS WITH ADDISON'S DISEASE

The circles indicate points at which pellets were removed, dried, weighed and reinserted.

in very good condition and it was calculated that the pellets *in situ* would provide adequate hormone therapy for a total of at least eight months.

Patient C. N. (see protocol), had been maintained in good condition for several months previous to this study by means of a single daily subcutaneous injection of 2–3 mg. of desoxy-corticosterone acetate in oil. No added sodium chloride therapy was required. On this regimen her weight was 58.8 kg., blood pressure 108/70 mm. Hg, plasma volume 2280 cc., hematocrit 39.7 per cent cells, plasma concentration of sodium 138.2 m.eq., of chloride 104.4 m.eq. and of potassium 6.6 m.eq. per liter. The blood non-protein nitrogen was 27 mg. per 100 cc. and the blood sugar (fasting) 80 mg. per 100 cc. At this time daily injections of desoxy-corticosterone acetate in oil were discontinued and on the same day four pellets of crystalline

TABLE 1

The effect on body weight of implantation of pellets of synthetic hormone

PATIENTS	BODY WEIGHT (KG.)		NUMBER OF DAYS FOLLOWING IMPLANTATION OF PELLETS
	Prior to implantation of pellets*	Following implantation of pellets	
	kg.	kg.	
M. M.	51.4	54.7	169
C. N.	56.8	61.0	80
J. Z.	42.3	44.6	50
P. W.	52.3	56.4	50
J. H.	65.5	70.0	40
D. B.	66.1	72.6	35

* The weights recorded in this column were the weights observed on the last day of treatment with injections of hormone in oil, with one exception, patient M. M., in whom pellets were inserted without preliminary treatment with daily injections of hormone.

hormone weighing 65.7, 69.0, 94.0 and 99.0 mg., respectively, were inserted subcutaneously in the infrascapular regions. Following the implantation of the pellets, the patient's general condition was very good and she was observed to be in positive sodium and chloride balance. Five weeks after the implantation of the pellets she weighed 62.5 kg., a gain of 3.7 kg. and her blood pressure was 114/72 mm. Hg. The plasma volume had increased from 2280 cc. to 2460 cc. and the plasma concentration of electrolytes was normal. At no time during this study was added sodium chloride therapy given. This patient had required a daily injection of 2–3 mg. of hormone in oil. The calculated quantity of hormone absorbed daily from the

pellets was approximately 1.3 mg. It appeared that the implantation of pellets effected at least a 30 per cent saving in hormone in addition to obviating the necessity for daily injections. This patient has now been maintained in very good condition for 3 months following a single implantation of four pellets. At present she is carrying on all of her household duties. On the basis of a calculated rate of absorption of 0.33 mg. per pellet per day, it seems probable that the present supply of pellets will provide adequate hormone for a total of six months.

Patient J. Z. (see protocol), had been treated with daily injections of desoxy-corticosterone acetate in oil for three months previous to the implantation of pellets. It was observed that 3.5 mg. daily of crystalline hormone in oil in addition to 12 gm. of sodium chloride were required to maintain him in good condition. On this regimen the patient weighed 42.3 kg., his blood pressure was 112/84 mm. Hg, plasma volume 2180 cc., hematocrit 36.0 per cent cells, plasma concentration of sodium 139.5 m.eq., of chloride 101.6 m.eq. and of potassium 5.0 m.eq. per liter, blood non-protein nitrogen 26 mg. per 100 cc. and blood sugar (fasting) 77 mg. per 100 cc. Daily injections of hormone in oil were discontinued and on the same day four pellets of desoxy-corticosterone acetate (63.1, 73.5, 76.6 and 86.4 mg. respectively) were implanted, the added sodium chloride therapy (12 gm. daily) being continued. Following the implantation of pellets the patient maintained a positive sodium and chloride balance, a normal blood pressure, a normal plasma volume and a normal plasma concentration of electrolytes.

Twenty-seven days after the implantation of the pellets, two were removed, weighed and reinserted. It was noted that one pellet had decreased from 86.4 mg. to 78.8 mg. (a loss of 7.6 mg.) and that a second had decreased from 73.5 mg. to 63.4 mg. (a loss of 10.1 mg.). These pellets had been absorbed at a rate of 0.28 mg. and 0.37 mg., respectively, per day or an average rate of 0.33 mg. daily. This rate of absorption corresponded closely to that observed in patient M. M. and to the rate of absorption observed in the experimental studies on adrenalectomized dogs (Chart 1). If it is assumed that the two remaining pellets were absorbed at the same average rate as those which

were removed and weighed, then the four pellets supplied approximately 1.3 mg. of hormone daily. This quantity of desoxy-corticosterone acetate was less than one-half of the required dose of hormone in oil injected once daily.

In addition to reinserting the two pellets removed for weighing, three additional pellets (weighing 87.0, 99.7 and 130.7 mg., respectively) were implanted, to provide additional hormone in preparing this patient for a nephrectomy since it was known that the right kidney was functionless and urine obtained from the right kidney contained tubercle bacilli. The implantation of the additional pellets not only

TABLE 2

The effect on the glucose tolerance of implantation of pellets of synthetic adrenal cortical hormone
(Patient J. Z.)

DATE 1939	BLOOD SUGAR, MG. PER CENT					TREATMENT
	Fasting	½ hr. after glucose*	1 hr.	2 hrs.	3 hrs.	
Feb. 13.....	82	87	82	69	63	14 days after the implantation of 4 pellets
Feb. 25.....	70	88	119	84	72	26 days after the implantation of 4 pellets
Mar. 16.....	74	166	132	56	54	45 days after the implantation of 4 pellets and 21 days after the implantation of 3 additional pellets

* 1.75 gm. of glucose per kilo of body weight were administered orally.

resulted in continued clinical improvement but also was accompanied by a remarkable change in the glucose tolerance curve (table 2).

Fifty days after the original implantation of pellets his weight was 44.6 kg., a gain of 3.1 kg., the blood pressure was 120/82 mm. Hg, hematocrit 34.6 per cent cells, and the plasma concentration of electrolytes was normal. At present the total daily quantity of hormone supplied by the seven pellets is calculated to be approximately 2.3 mg. daily. Although the seven pellets represent a greater-than-maintenance dose the quantity of hormone absorbed is still considerably less (30 per cent) than the previously determined daily requirement of hormone in oil (3.5 mg.). Due in part to the 3 large pellets inserted 27 days after the original insertion of the four pellets, it seems

likely that adequate hormone will be provided for at least seven months from the time of initial implantation.

The clinical condition of this patient is so satisfactory at this time that removal of the right kidney is being contemplated in an effort to eradicate an active focus of tuberculosis.

Patient P. W. (see protocol), required a daily injection of 5 mg. of desoxy-corticosterone acetate in oil, in addition to 12 gm. of sodium chloride orally. On this regimen the patient weighed 52.3 kg., his blood pressure was 114/84 mm. Hg, hematocrit 34.5 per cent cells, plasma volume 2720 cc., plasma concentration of sodium 138.0 m.eq., of chloride 100.4 m.eq. and of potassium 6.2 m.eq. per liter, blood non-protein nitrogen 27 mg. per 100 cc. and blood sugar (fasting) 68 mg. per 100 cc. Injections of desoxy-corticosterone acetate in oil were discontinued and on the same day six pellets (62.2, 66.3, 67.8, 73.0, 77.8 and 93.3 mg., respectively) of synthetic hormone were implanted in the infraclavicular region, the added sodium chloride (12 gm. daily) being continued. Following this, the patient was maintained in excellent condition. He gained weight (4.1 kg.) and his blood pressure increased from 114/84 to 122/92 mm. Hg. A positive sodium and chloride balance was noted as well as a normal plasma volume and a normal concentration of plasma electrolytes. Two months after the pellets had been inserted this patient was observed to be in very good condition and leading an active life. If the rate of absorption (approximately 0.33 mg. per pellet per day) noted in two of the patients and in the experimental animals is assumed to have obtained for this patient, then a total of 2.0 mg. of hormone are being absorbed daily. This quantity of hormone is less than 50 per cent of the dose of hormone in oil required for maintenance under similar conditions. It is estimated that the present supply of pellets in this patient will suffice for at least a total of six months.

Patient J. H. (see protocol), had been maintained in fair condition by means of large quantities (20–40 cc.) of adrenal cortical extract[3] in glycerin administered orally and 10 grams of sodium chloride daily. On this regimen the patient's weight was 63.0 kg., his blood pressure 100/56 mm. Hg, hematocrit 41.0 per cent cells, plasma concentration

[3] Wilson and Company Adrenal Cortical Extract.

of sodium 126.7 m.eq., of chloride 95.2 m.eq. and of potassium 8.2 m.eq. per liter, blood non-protein nitrogen 55 mg. per 100 cc. and blood sugar (fasting) 83 mg. per 100 cc. Twelve days after treatment with injections of desoxy-corticosterone acetate in oil, 5–20 mg. daily, had been instituted the patient had gained 2.5 kg. in weight, his blood pressure had increased from 100/56 to 110/70 mm. Hg, the hematocrit was 35.3 per cent cells, the plasma concentration of sodium 136.9 m.eq., of chloride 105.6 m.eq. and of potassium 6.2 m.eq. per liter, the blood non-protein nitrogen 31 mg. per 100 cc. and the blood sugar (fasting) 80 mg. per 100 cc. During this period of improvement the added sodium chloride treatment (10 gm. daily) was continued.

TABLE 3

The effect of synthetic adrenal cortical hormone on blood pressure

PATIENTS	BLOOD PRESSURE, MM. Hg*		
	Before treatment with synthetic hormone	After treatment with injections of synthetic hormone in oil	After implantation of pellets of synthetic hormone
M. M.	85/72		114/76—169 days
C. N.	94/60	108/70	112/78— 80 days
J. Z.	85/60	112/82	120/82— 50 days
P. W.	95/60	114/84	122/90— 50 days
J. H.	100/56	110/70	135/80— 40 days
D. B.	108/70	114/78	130/80— 35 days

* The blood pressure measurements were made at 7 a.m. with the patients resting quietly in bed. They represent the average of three determinations made on three successive days during the period indicated.

Later it was possible to maintain this patient in good condition by means of a single daily injection of 5 mg. of desoxy-corticosterone in oil in addition to 10 gm. daily of sodium chloride. At this time injections of hormone in oil were discontinued and, on the same day, six pellets of crystalline desoxy-corticosterone acetate (48.2, 74.9, 77.5, 85.8, 90.7 and 90.7 mg., respectively) were implanted, the added sodium chloride therapy being continued. The subsequent improvement of this patient was remarkable. A positive sodium and chloride balance was maintained and two weeks after the insertion of pellets he weighed 68.0 kg. (a gain of 2.5 kg.) and his blood pressure was 130/90 mm. Hg. Forty days after the pellets were implanted he

weighed 70.0 kg., (a total gain of 5.5 kg.). His blood pressure was 135/90 mm. Hg, the hematocrit 41.7 per cent cells, the plasma concentration of sodium 141.7 m.eq., of chloride 104.5 m.eq. and of potassium 5.5 m.eq. per liter. The blood non-protein nitrogen was 25 mg. per 100 cc. and the blood sugar (fasting) 89 mg. per 100 cc. At this

TABLE 4

The effect of synthetic adrenal cortical hormone in Addison's disease

(Patient D. B.)

	ADRENAL CORTICAL EXTRACT[4] 2 CC. T.I.D.	DESOXY-CORTICO-STERONE ACETATE, 5 MG. DAILY, IN OIL	HORMONE THERAPY DISCON-TINUED	PELLETS OF SYNTHETIC HORMONE IMPLANT-ATED ON FEB. 13TH
	Date			
	Jan. 25-30	Jan. 30-Feb. 8	Feb. 8-13	Feb. 13-24
Body weight, kg.	64.7	66.3	65.5	68.3
Blood pressure, mm. Hg.	108/70	114/78	112/76	130/80
Hematocrit, per cent cells	44.2	41.7	45.0	39.7
Plasma, vol. cc	2870	3090	2760	3380
Total blood volume				
a) in cc	5140	5300	5020	5600
b) in % normal	93.5	96.0	91.5	100.0
Plasma Na, m.eq. per liter	143.2	139.0	135.5	138.1
Plasma Cl, m.eq. per liter	100.8	102.8	97.8	105.6
Plasma K, m.eq. per liter	4.0	5.8	5.4	4.0
CO_2 combining power, vol. %	52.2	57.0	58.7	63.6
Non-protein nitrogen, mg. per cent	32	28	30	28
Blood sugar, mg. %	80	73	84	85
Sodium balance, m.eq./24 hr	+9.0	+103.4	−19.9	+77.0
Chloride balance, m.eq./24 hr	+2.4	+62.8	−19.9	+41.4
Urinary excretion of K, m.eq./day	65.5	71.5	55.0	63.2
Urinary excretion of inorganic P, gm./day	0.88	0.73	0.76	0.73

time he had improved sufficiently so that he was able to return to his former occupation as clerk.

It was calculated that the six pellets which were implanted provided approximately 2.0 mg. daily of desoxy-corticosterone acetate. This represented a great saving in comparison to the maintenance dose of desoxy-corticosterone acetate in oil (5 mg. daily). The implantation of these pellets should provide adequate hormone therapy for approximately six months.

Patient D. B. (see protocol), had been maintained in fair condition by means of 12 gm. of sodium chloride daily, administered orally, and 2 cc. of adrenal cortical extract,[4] injected subcutaneously three times daily. On this regimen the patient weighed 64.5 kg. and his blood pressure was 108/70 mm. Hg. The hematocrit was 44.2 per cent cells, the plasma volume 2870 cc., the plasma concentration of sodium 134.2 m.eq., of chloride 100.8 m.eq., and of potassium 4.0 m.eq. per liter. The blood non-protein nitrogen was 32 mg. per 100 cc. and the blood sugar 80 mg. per 100 cc. A single daily injection of 5.0 mg. of desoxy-corticosterone acetate in oil was substituted for the three injections of adrenal cortical extract, the added sodium chloride therapy (12 gm. daily) being continued. During a five day period on this treatment (table 4) he gained 1.3 kg., his blood pressure increased to 114/78 mm. Hg, the plasma volume increased from 2870 cc. to 3090 cc. and the hematocrit decreased from 44.2 per cent to 41.7 per cent. The plasma concentration of sodium increased from 134.2 m.eq. to 139.0 m.eq. and the plasma chloride increased from 100.8 to 102.8 m.eq. per liter. During this period there occurred a marked retention of sodium and chloride (table 4). After five days of treatment with injections of desoxy-corticosterone acetate in oil, the hormone therapy was discontinued, the added sodium chloride therapy, however, being maintained. The patient then lost 0.8 kg. in weight in 5 days, and a marked increase in the renal excretion of sodium and chloride was noted. The plasma concentration of sodium decreased from 139.0 m.eq. to 135.5 m.eq. and the plasma chloride concentration decreased from 102.8 to 97.8 m.eq. The plasma volume was reduced from 3090 cc. to 2760 cc. and the hematocrit increased from 41.7 per cent to 45.0 per cent cells. At this time four pellets of crystalline desoxy-corticosterone (83.7, 111.8, 119.5 and 137.2 mg. respectively) were implanted, the added sodium chloride therapy remaining unchanged (chart 2).[5]

Eleven days after the implantation of pellets, the patient had gained 2.1 kg., his blood pressure was 130/80 mm. Hg, the plasma volume had increased from 2760 cc. to 3380 cc. and the hematocrit had decreased

[4] Upjohn and Company, adrenal cortical extract.

[5] During the study shown in chart 2 the patient was provided with a diet which contained by analysis 331.5 m.eq. of sodium and 54.5 m.eq. of potassium.

from 45.0 per cent to 39.7 per cent cells. During this period the patient again retained large quantities of sodium and chloride (table

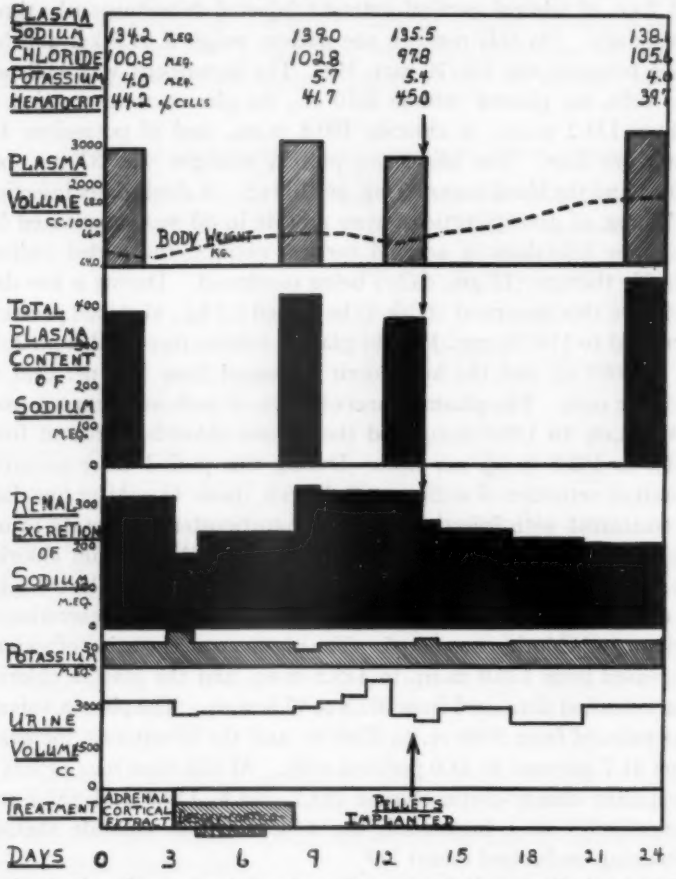

CHART 2. THE EFFECT OF PELLETS OF SYNTHETIC HORMONE (PATIENT D. B.)

4). The concentration of plasma electrolytes returned to normal and his clinical improvement was striking.

The changes in plasma volume and in the total plasma content of sodium (chart 2) paralleled very closely the changes which were observed in the clinical condition of this patient.

Following the implantation of pellets, the patient gained 2.8 kg. in weight and retained a total of approximately 770 m.eq. of sodium in eleven days. This retention exceeded by approximately 350 m.eq. the quantity of sodium which would be required for an increase of extracellular fluid of 2.8 liters and for an increase in the concentration of sodium from 135.5 m.eq. to 138.1 m.eq. per liter. Such an increase in the quantity of sodium retained might be accounted for by a shift of fluid from cells to the extracellular compartment. The increased renal excretion of potassium (a total of 90 m.eq. in eleven days) which occurred in this patient during this same period also suggests that a change in the distribution of water and electrolytes between cells and extracellular spaces may have occurred. A shift of fluid from cells to the extra-cellular compartment has been observed by Harrop (4) in adrenalectomized dogs given large quantities of adrenal cortical hormone.

To prepare this patient for resumption of his occupation as a mechanic which involves moderately heavy work, three additional pellets weighing 105.2, 114.7 and 137.0 mg., respectively, were inserted 25 days after the original implantation of pellets. Ten days later the patient weighed 72.6 kg., a total gain of 6.5 kg., his blood pressure was 130/80 mm. Hg, and he appeared to be in excellent condition. It was calculated that the seven pellets provided approximately 2.3 mg. of hormone daily which represented a considerable economy in comparison to the daily requirement of 5 mg. of hormone in oil. It is estimated that the seven pellets which were inserted in this patient will provide adequate hormone therapy for at least 9–10 months.

DISCUSSION

The determination of a patient's daily requirement of synthetic hormone has been found to be of great assistance in the successful treatment of Addison's disease with pellet implants of crystalline hormone. Such an assay provides an opportunity for demonstrating the efficacy and necessity for hormone therapy and is a requisite for calculating accurately the number of pellets which are needed for maintenance. It has been observed that one pellet of 100–150 mg. is required for each 0.5 mg. of hormone in oil necessary for satisfactory maintenance on the same regimen.

Pellets of synthetic hormone inserted subcutaneously cause no local discomfort or reaction. Upon removal they are usually found to be encapsulated in a thin, fibrous membrane. Pellets weighing 50–150 mg. are absorbed at a rate of 0.25–0.35 mg. per day. It is desirable to insert pellets of a standard size (125–150 mg.), obtaining varying concentrations of hormone by increasing or decreasing the number of pellets rather than by varying the size. The size of the pellets has been limited by the amount of synthetic hormone available. The hormone requirement of a patient does not appear to modify the rate of absorption. In the absence of fragmentation, the uniform rate of absorption observed in dogs and human subjects indicates that absorption follows physical laws. The maintenance of a rather constant rate of absorption as a pellet decreases in size is probably accounted for by either a softening of the pellet which would result in more rapid absorption, or canalization which would offer a greater surface for absorption. The fact that a prolonged period exists during which absorption is so constant greatly favors the practical applicability of this technic.

Pellet implants provide a constant supply of hormone and for this reason this form of treatment is recommended as substitution therapy in patients who have been restored to some degree of health by means of treatment with daily injections of hormone. Pellet implants alone are not a suitable form of treatment for patients in crisis. It may be necessary to supplement pellet therapy with (*a*) injections of hormone in oil, (*b*) an increase in the intake of sodium chloride, (*c*) a reduction in potassium intake during the course of an acute infection.

Loeb, Atchley, Benedict and Leland (5) and Harrop, Soffer, Ellsworth and Trescher (6) demonstrated the close relationship between the function of the adrenal cortex and the regulation of sodium metabolism. Truszkowski and Zwemer (7) and Wilder, Kendall, Snell, Kepler, Rynearson and Adams (8) have pointed out the correlation between the signs and symptoms of adrenal insufficiency and disorders in potassium metabolism. It has been suggested by Swingle, Parkins, Taylor and Hays (9) that the adrenal cortical hormone is concerned primarily with the regulation of plasma volume and blood pressure. Britton and Silvette (10) express the opinion that in adrenal insufficiency the disturbance in the regulation of carbohydrate metabolism is a primary change.

It is of considerable interest to note that treatment with a crystalline, synthetic compound, desoxy-corticosterone acetate, will (*a*) maintain adrenalectomized dogs in good condition on a diet of low sodium chloride and high potassium content (11), (*b*) result in sodium and chloride retention and the restoration of the plasma concentration of these ions to normal (2, 3, 11, 12), (*c*) result in a potassium diuresis and reduce the increased plasma concentration of potassium to normal (2, 3, 11, 12), (*d*) restore plasma volume and correct the existing dehydration, (*e*) result in weight gain and a marked increase in the blood pressure of patients with Addison's disease, and (*f*) result in great improvement in carbohydrate metabolism (Thorn and Kuhlman, to be published). It also appears likely that treatment with this compound results in an internal shift of water (patient D. B. in text).

It cannot be stated from the evidence presented, which, if any, of these changes is primary. It can be readily shown, however, that alterations in the plasma volume and in the renal excretion of sodium, chloride and potassium, are the first demonstrable changes following hormone withdrawal or replacement.

Although, to date, the complete disappearance of the increased pigmentation has not been observed in any patient treated with the synthetic hormone, some decrease in pigmentation has occurred in patients M. M., J. Z., P. W. and J. H.

SUMMARY

The subcutaneous implantation of pellets of synthetic adrenal cortical hormone was followed by striking and continued improvement in six patients with Addison's disease. The implantation of pellets of desoxy-corticosterone acetate resulted, in all of the patients, in changes similar to those previously observed following a daily injection of the hormone in oil, *i.e.*, a positive sodium and chloride balance, an increase in the concentration of these ions in the blood plasma, an increased renal excretion of potassium, an increase in plasma volume, a gain in body weight, an increase in blood pressure and a return to normal activity. In one patient who had an abnormal glucose tolerance curve, continued treatment with pellet implants was associated with a marked change toward normal.

Pellets of synthetic hormone are slowly absorbed and thus exert a prolonged effect. The implantation of pellets of synthetic hormone

obviates the necessity for daily injections of hormone and, in addition, effects a great economy in the use of hormone. It is desirable to determine first a patient's daily requirement of hormone in oil, injected subcutaneously or intramuscularly, before pellets are implanted. Pellet implants of crystalline hormone appear to be the most efficacious and economical method available for administering adrenal cortical hormone.

The authors are indebted to Miss Mildred Caldwell, Supervisor of the Metabolism Ward, Miss Elizabeth Olsen, Dietician-in-charge of the Metabolism Ward, Mrs. Florence White of the Bio-chemical Laboratory of the Johns Hopkins Hospital, Harry Eisenberg, Kay Eisenberg and William Sause of the Chemical Division of the Department of Medicine, Johns Hopkins Medical School for their technical assistance and continued coöperation.

CASE PROTOCOLS[6]

M. M. (no. 107577) a 27 year old housewife, was first admitted to the Johns Hopkins Hospital on May 11, 1937 because of vomiting and weakness. The present illness began in March, 1937, with a gradual onset of weakness and fatiguability. In April she began to have mild anorexia, nausea and persistent vomiting, which continued up to the time of her admission. During this illness she lost 7.2 kg. in weight and became so weak that she was unable to leave bed. One month prior to admission she noticed some darkening of her skin. The family and past history were non-contributory. During childhood the patient had had measles, chickenpox and pertussis. There was no history of tuberculosis. Menses had always been normal and remained so throughout her illness. She had had one normal pregnancy in 1933.

Physical examination on May 11, 1937, revealed a well developed, fairly well nourished white woman, appearing extremely weak and exhausted. Her temperature was 98.2°F., pulse rate 70 per minute, respirations 14 per minute, blood pressure 82/62 mm. Hg, and weight 53.1 kg. The skin was evenly pigmented, light brown in color. In the creases of the palms, knuckles and axillae, about the areolae of the breasts and along the mid-abdominal line there was definite dark brown pigmentation. Over the face, palms and back were several small darkly pigmented nevi. There was no pigmentation of the mucous membranes. The thyroid was very slightly enlarged without thrill or bruit. The heart sounds were distant and muffled, and a soft systolic murmur was heard at the base and apex. Otherwise the physical examination revealed no abnormalities.

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[6] A detailed account of the treatment of patients C. N., P. W. and J. Z. with injections of desoxy-corticosterone acetate in oil is contained in the publication referred to in the bibliography (3).

The laboratory examinations were as follows: Hb. 120 per cent, r.b.c. 6.19 million (hemoconcentration), w.b.c. 13,650, polymorphonuclears 79 per cent, eosinophiles 2 per cent, lymphocytes 17 per cent, monocytes 2 per cent, cell volume 50 per cent, sedimentation rate 8 mm. in 1 hr. The blood Wassermann test was negative. Chemical examination of the blood revealed: non-protein nitrogen 24 mg. per 100 cc., sugar 84 mg. per 100 cc., plasma sodium 109.6 m.eq., plasma chloride 71.8 m.eq. per liter and total plasma protein 6.3 gm. per 100 cc. The specific gravity of the urine was 1.010, and acetone and diacetic acid were present. X-ray pictures of the chest and abdomen revealed no evidence of tuberculosis or adrenal calcification.

The patient was started immediately on sodium chloride therapy intravenously and by mouth. She improved rapidly. In 48 hours she was able to retain food, her blood pressure had risen to 104/68 mm. Hg and the plasma concentrations of sodium and of chloride were 123 and 90.6 m.eq. per liter, respectively. Subcutaneous injections of adrenal cortical extract[3] were started on May 13th in conjunction with a high sodium chloride and a high carbohydrate diet. Steady improvement continued and on May 20, 1937 the plasma electrolytes had reached normal levels. Her strength and appetite increased steadily, and the patient was discharged on June 16th weighing 53.4 kg. She was given a maintenance dose of 2 cc. of injected cortical extract twice daily in addition to a high sodium chloride and carbohydrate intake.

On this regimen she remained well, maintained her weight and strength and was able to do her housework until August 11, 1937, when she had a sudden attack of diarrhea and fever and was readmitted to the hospital. At this time her blood pressure was 84/46 mm. Hg. The plasma concentration of sodium was 131.5 m.eq. and of chloride 100 m.eq. per liter. Following the injection of increased quantities of extract subcutaneously and of saline and glucose solution intravenously, the fever and diarrhea ceased after 3 days. On Aug. 17th, her blood pressure was 88/64 mm. Hg, the plasma concentration of sodium was 135.1 m.eq. and of chloride 104.4 m.eq. per liter. She was discharged on Aug. 19th, weighing 55.1 kg.

She continued to feel fairly well on 4 cc. (160 gm. of adrenal cortex) of injected extract and 10 gm. of sodium chloride daily. On Sept. 18th, oral extract was substituted for injected.[7] Her good health continued, she successfully passed through two severe attacks of tonsillitis without change in medication. On April 12, 1938, plasma concentration of sodium was 141.7 m.eq. and chloride 103.2 m.eq. per liter.

On June 10, 1938, the oral extract was discontinued and the patient was given a total of 9.9 mg. of crystalline desoxycorticosterone acetate in the form of a hand packed pellet injected subcutaneously through an 18 gauge needle. At this time her weight was 54.5 kg., blood pressure 104/55 mm. Hg, plasma con-

[7] Wilson and Company adrenal cortical extract added to glycerol.

centration of sodium 137.8 m.eq. and of chloride 101.0 m.eq. per liter. On June 15th another pellet weighing 4.5 mgm. was similarly injected. The previous intake of 10 gm. of sodium chloride was continued. During the following 6 weeks she continued to feel well and maintained her weight. The plasma sodium and chloride concentrations remained normal. Two and one half months after the injection of the crystalline hormone there was first noted gradually increasing weakness, failing appetite and a slight fall in blood pressure. On September 17, 1938, 3 months after the synthetic hormone had been injected, the plasma concentration of sodium was 134.7 m.eq. per liter and of chloride 102.8 m.eq. per liter. No significant change in body weight had occurred. During the following 3 weeks there was a rapid increase in weakness and anorexia. The patient's weight decreased to 51.2 kg. and the plasma concentration of sodium was found to be 131.4 m.eq. and the chloride 96.2 m.eq. per liter. On October 9, 1938, the patient was readmitted for implantation of more pellets of desoxy-corticosterone acetate. The subsequent treatment and changes observed are recorded in the text.

C. N. (no. 100114), a married, female telephone operator, 34 years of age, was admitted to the Johns Hopkins Hospital on June 3, 1936 complaining of weakness, weight loss, nausea and vomiting. Three years before admission the patient had noticed increasing fatigue and some darkening of her skin. For two weeks before admission nausea had been present almost constantly and the patient had been confined to bed. During her illness she had lost 15.9 kg. in weight. Until the present illness her menses had been normal. For one year prior to admission her menses had been irregular. In 1932 and again in 1933 she had had a peritonsillar abscess.

Physical examination on admission, June 2, 1936, revealed a pale woman who appeared to be rather weak and showed evidence of considerable weight loss. Her temperature was 97.2°F., pulse rate 82, respirations 20 and blood pressure 86/60 mm. Hg. Her skin was slightly tanned. There was dark pigmentation of the borders of the lips and a large blotchy brown area over the lower left abdomen. The hearts sounds were distant and of poor quality, and the radial pulses were feeble. Otherwise the physical examination was normal.

The laboratory findings were as follows: Hgb. 106 per cent, r.b.c. 5.3 million (hemoconcentration), w.b.c. 12,750, polymorphonuclears 64 per cent, lymphocytes 26 per cent, monocytes 7 per cent, eosinophiles 2 per cent, basophiles 1 per cent, cell volume 48 per cent, blood Wassermann test negative, non-protein nitrogen 46 mg. per 100 cc., sugar 80 mg. per 100 cc., plasma sodium concentration 138.9 m.eq. per liter and the B.M.R. −11 per cent. The urine was normal.

A trial of salt deprivation was begun, and in 3 days a typical Addisonian crisis occurred. Plasma sodium concentration fell from a level of 138.9 m.eq. to 124 m.eq. per liter; and the patient became semicomatose, the blood pressure being 66/44 mm. Hg. Rapid recovery followed the administration of cortical extract

and the intravenous infusion of sodium chloride and glucose. The patient was discharged on June 20, 1936, feeling somewhat weak but otherwise improved.

During the next year the patient continued to be in fair health although she was never strong enough to do her housework. On Aug. 28, 1937 she was admitted to the hospital in a crisis. Following large amounts of salt, glucose and extract by vein and subcutaneously she improved rapidly and remained well on injected extract and a high salt (10–12 gm. NaCl daily) and carbohydrate intake.

Since Sept. 18, 1937 extract[7] had been administered orally rather than by injection. Her health continued to improve, and 5 months later she was able to return to her former work on a part-time basis in addition to doing her own housework and gardening. On October 17, 1938 she was readmitted for trial of desoxy-corticosterone acetate therapy.

Résumé of treatment with desoxy-corticosterone acetate in oil. On admission, blood examination revealed the following values: serum sodium 131.4 m.eq., serum chloride 95.0 m.eq., and serum potassium 5.00 m.eq. per liter, carbon dioxide combining power 56.0 volumes per cent, non-protein nitrogen 40 mg. per 100 cc., sugar 78 mg. per 100 cc. and total protein 6.88 gm. per 100 cc. Desoxy-corticosterone acetate (10–15 mg. daily) was substituted for the orally administered extract, the sodium chloride therapy being continued. The substitution of desoxy-corticosterone acetate treatment (sodium chloride 15 gm. daily being continued) resulted in marked clinical improvement, an increase in blood pressure, a very marked retention of sodium and chloride and a striking gain in weight. On the 7th day of treatment, doubtless as a result of the retention of sodium, moderate edema of the face and extremities was apparent. Withdrawal of desoxy-corticosterone acetate treatment (sodium chloride 15 gm. daily being continued) resulted in a marked diuresis and weight loss, and, after 72 hours, in loss of appetite and strength. Resumption of desoxy-corticosterone acetate treatment (5–10 mg. daily) resulted in prompt improvement and again was accompanied by a marked gain in weight. At this time the added sodium chloride therapy (15 gm. daily) was entirely discontinued and the patient was treated with desoxy-corticosterone acetate (5 mg. daily) only. This patient has been maintained in good condition for four months by means of desoxy-corticosterone acetate treatment (2–5 mg. daily) without added sodium chloride therapy. Subsequent observations following the implantation of pellets, are given in the text.

J. Z. (no. 155645), a 19 year old Italian boy, was admitted to the Johns Hopkins Hospital on October 27, 1938 with a diagnosis of Addison's disease. His illness began in the spring of 1936 with the gradual onset of loss of strength, appetite and weight, and a slowly progressive generalized brown pigmentation of the skin. In September 1936 he began to have persistent vomiting. At this time a diagnosis of Addison's disease was made and treatment with sodium chloride and adrenal cortical extract was begun. He improved promptly and since that time has been maintained in fair health on a high sodium chloride intake and 1–2 cc. of adrenal

cortical extract[3] (40–80 gms. fresh adrenal cortex) daily, injected subcutaneously. On several occasions during the past 2 years he has required intravenous saline, and has continued to be markedly underweight. In 1937 tubercle bacilli were found in his urine. During his illness the patient had lost 25 pounds in weight.

In 1928 the patient's brother died of tuberculosis, and in 1930 his mother died of the same disease. Another brother and sister were sent to a preventorium in in 1933 as tuberculosis suspects, although the disease was never proved in these siblings.

Physical examination on admission, Oct. 27, 1938, revealed a thin, poorly nourished and underdeveloped white boy appearing weak and tired. His temperature was 99.4°F., pulse rate 88 per minute, respirations 18 per minute and blood pressure 90/50 mm. Hg. The skin was dry and pale and there was generalized diffuse brownish pigmentation over the neck, trunk and extremities becoming almost black over the knees, thighs and gluteal folds. Small cervical and axillary lymph nodes were palpable but there was no general glandular enlargement. The lungs were clear and the heart normal.

The laboratory data on admission were as follows: hgb. 48 per cent (11.5 gms.), r.b.c 3.69 millions, hematocrit 34 per cent cells, w.b.c. 4,760 with polymorphonuclears 68 per cent, lymphocytes 24 per cent, monocytes 8 per cent. The sedimentation rate was 25 mm. in 1 hour, corrected. The blood Wassermann was negative. The blood non-protein nitrogen was 40 mg. per 100 cc. and the blood sugar 70 mg. per 100 cc. The serum CO_2 combining power was 43.8 vol. per cent, the plasma concentration of sodium 131.2 m.eq., chloride 91.8 m.eq. and potassium 6.1 m.eq. per liter. The total serum protein was 7.2 gm. per 100 cc.

The urine was found to have a specific gravity of 1.020, and contained a trace of albumen and many leucocytes but no red cells or casts. Acid fast bacilli were obtained from urine specimens both by culture and guinea pig inoculation.

An x-ray picture of the chest showed "inactive" fibroid infiltration at the left apex. In a flat plate of the abdomen, calcium shadows were visible in both suprarenal regions and x-ray pictures of the skull showed numerous areas of increased density scattered throughout the brain which were interpreted as being healed tubercles.

The basal metabolic rate was plus 18 per cent. On Dec. 17, a phenolsulphthalein test showed a dye excretion of 30 per cent in 30 minutes and 52 per cent at the end of two hours. An electrocardiogram gave a normal tracing.

Résumé of treatment with desoxy-corticosterone acetate in oil. Because of the presence of an active tuberculous lesion of the urinary trect and the very poor clinical condition of the patient 15 gm. of added sodium chloride were continued during the institution of desoxy-corticosterone acetate treatment (20–30 mg. daily). This treatment resulted in marked improvement in the patient's general condition, increased appetite and sense of well-being, marked increase in weight and increased blood pressure. Two weeks after desoxy-corticosterone acetate treatment had been instituted, the added sodium chloride was entirely discontinued, the patient's progress being maintained successfully by means of desoxy-

corticosterone acetate treatment alone. Subsequently, withdrawal of desoxy-corticosterone acetate treatment resulted in a rapid onset of the symptoms of adrenal insufficiency. At this time resumption of desoxy-corticosterone acetate treatment, without added sodium chloride, resulted in marked improvement in the patient's clinical condition.

After being maintained successfully for 20 days by means of desoxy-corticosterone acetate treatment alone an attempt was made to determine the requirement of hormone when sodium chloride treatment was added. It was found that a single daily injection of 5 mg. of desoxy-corticosterone acetate daily was sufficient for this patient when 15 gm. of sodium chloride were added to his diet. Subsequent observations are recorded in the text.

P. W. (no. 150453), a 34 year old clergyman was admitted to the Johns Hopkins Hospital on October 5th, 1938 for treatment of Addison's disease. Generalized brownish pigmentation was first noticed in 1925. In the summer of 1932–33 he had heat cramps which were relieved by salt water. In 1934 he had an attack of nausea, vomiting and weakness, progressing to coma. At this time he was found to have a blood pressure of 70/50 mm. Hg. Treatment with sodium chloride, glucose and adrenal cortical extract resulted in marked improvement and since then he has been maintained in fair health on small doses of cortical extract[3] (2–3 cc. daily representing approximately 80–160 gm. fresh cortex) and 8–10 gm. of added sodium chloride daily. On two occasions he has been on the verge of collapse necessitating intravenous therapy.

In 1930 the patient had a severe sore throat; in 1932 a tonsillectomy was performed, and in 1934 he underwent an appendectomy.

On October 5, 1938 physical examination revealed a white male of slight build, fairly well nourished, appearing alert, and in no discomfort. The temperature was 98.2°F., pulse rate 84 per minute, respirations 22 per minute and blood pressure 94/60 mm. Hg. The skin was slaty brown in color with dark brown pigmentation of the face, neck, forearms, external genitalia and gluteal folds. Over the face, neck and shoulders were a few scattered deeply pigmented nevi. No pigmentation of the mucous membranes was observed. The external ears were hard and cartilagenous. The lungs were clear and the heart was normal save that the heart sounds were distant.

Laboratory data on admission were as follows: r.b.c. 4.3 millions, hgb. 12.7 gms., w.b.c. 5,000 with polymorphonuclears 69 per cent, lymphocytes 25 per cent and monocytes 6 per cent. The sedimentation rate was 12 mm. in 1 hour and the volume of packed r.b.c. 43 per cent. The blood Wassermann was negative. The blood non-protein nitrogen was 38 mg. per 100 cc., blood sugar 65 mg. per 100 cc., plasma CO_2 combining power 57.9 vol. per cent, plasma concentration of sodium 130.5 m.eq., of chloride 97.8 m.eq. and potassium 5.2 m.eq. per liter, and total plasma protein 7.38 gms. per cent. Examination of the urine was negative.

The basal metabolic rate was plus 4 per cent. X-rays of the heart and lungs

were normal. There was no evidence of calcification in the area of the adrenals. An electrocardiographic tracing showed T1 to be isoelectric and T2 and T3 to be inverted.

Résumé of treatment with desoxy-corticosterone acetate in oil. Withdrawal of sodium chloride and extract treatment (for 48 hours) resulted in the onset of symptoms of acute adrenal insufficiency associated with a marked lowering of blood pressure, anorexia, vomiting, a diuresis associated with an increased excretion of sodium and chloride, a further lowering of the serum concentration of sodium and chloride and a slight rise in the serum concentration of potassium. At this time 15 mg. of desoxy-corticosterone acetate were injected and the patient was given a single infusion of 16 gm. of sodium chloride (a quantity of sodium chloride calculated to be equivalent to the negative balance of sodium chloride which had obtained during the 2 days without treatment). Subsequently, the patient received 15–20 mg. of desoxy-corticosterone acetate daily, no additional sodium chloride being given. The patient was maintained on this regimen for 23 days with marked clinical improvement, increased appetite, gain in body weight and increased blood pressure.

At this time it was decided to test the dose of desoxy-corticosterone acetate which would be required when sodium chloride therapy (15 gm. daily) was added to the regimen. Previous experience had shown that this patient could not be adequately maintained on sodium chloride therapy alone. Following the addition of 15 gm. of sodium chloride to the diet it was observed that approximately 5–6 mg. daily of desoxy-corticosterone acetate were sufficient to maintain him in excellent condition. Subsequent observations following implantation of pellets are recorded in the text.

J. H. (no. 160819), a 22 year old white male, was admitted to the Johns Hopkins Hospital on January 30, 1939, complaining of weakness, loss of appetite and discoloration of his skin. His present illness began during the winter of 1938 when the patient first noted slowly increasing weakness. In May 1938 there developed rather abruptly headache and marked anorexia. At the same time generalized darkening of the skin became manifest. The patient was found to have a persistent low-grade fever and subsequently developed general glandular enlargement. He was taken to a hospital where a diagnosis of Addison's disease was made, and confirmed by laboratory findings. In addition, the typical blood picture of infectious mononucleosis was discovered and the heterophile antigen agglutinations were found to be positive in dilutions of 1:64. The administration of large quantities of salt and adrenal cortical extract orally[7] and parenterally[3] resulted in considerable improvement. He remained in fair health except for an acute attack of serum sickness in August 1938 following an injection of tetanus antitoxin, when his temperature rose to 105°F. and he became comatose and went into shock. With intravenous salt solution and large amounts of cortical extract parenterally he made a rapid recovery.

The family history and the patient's past history were non-contributory.

Physical examination on admission January 30, 1939, revealed a thin, but well developed, rather tired young man not acutely ill. His temperature was 98.6°F., pulse 84 per minute, respiratory rate 18 per minute and blood pressure 92/50 mm. Hg. He weighed 63.2 kg. The skin of his whole body was deeply tanned, with numerous black freckles over the back. Some bluish mottling was present along the gum margins. The thyroid was not enlarged and the lymph glands were normal. The lungs were clear, and the heart normal except for a blowing systolic murmur at the apex. The remainder of the physical examination was normal.

The laboratory findings were as follows: Hgb. 93 per cent, r.b.c. 4.53 million, cell volume 41 per cent, w.b.c. 9,700, polymorphonuclears 47 per cent, lymphocytes 43 per cent, monocytes 9 per cent and eosinophiles 1 per cent. There were numerous abnormal lymphocytes resembling those seen in infectious mononucleosis. The blood Wassermann reaction was negative. The blood chemical determinations noted at this time are given in the text. Urine examination revealed a specific gravity of 1.020, a very faint trace of albumen and no sugar. The sediment contained an occasional red and white cell but no casts. X-ray pictures of the chest and abdomen were normal. The basal metabolic rate was plus 7 per cent. The subsequent treatment, and the changes observed are given in the text.

D. B. (no. 160799), a 33 year old married white man was admitted to the Johns Hopkins Hospital on January 28, 1939, complaining of weakness and darkening of his skin. His present illness began in June 1938 when weakness and increasing pigmentation of the skin were first noted. In November 1938 he began to suffer from attacks of faintness and nausea. During December of the same year the pigmentation of his skin increased rapidly and a diagnosis of Addison's disease was made. He was given large quantities of salt and fruit juices by mouth and 3 cc. daily of cortical extract[4] subcutaneously. Improvement in strength and some decrease in pigmentation followed promptly, although considerable residual weakness remained. During his illness the patient lost 9 kg. in weight.

The family history was non-contributory and the patient's past health had always been excellent. As a child he had had measles, mumps, whooping cough and scarlet fever. There was no history of exposure to tuberculosis. In 1928 a right inguinal hernia had been repaired and in 1930.

Physical examination on admission revealed a very well developed, fairly well nourished man, appearing weak and tired but not acutely ill. His temperature was 99.2°F., pulse 74 per minute, respirations 18 per minute and blood pressure 115/75 mm. Hg. There was a striking diffuse dark brown pigmentation of the skin over the entire body, being almost black in the perineal region. Many black nevi were scattered over the neck and back, and the gums and buccal mucous membranes were discolored with a mottled bluish-black pigmentation. The thyroid gland was normal in size and there was no general glandular enlarge-

ment. The heart and lungs were normal and except for external hemorrhoids no other abnormalities were noted on physical examination.

The laboratory findings on admission were as follows: Hgb. 95 per cent, r.b.c. 5.0 million, w.b.c. 8,400, polymorphonuclears 67 per cent, eosinophiles 10 per cent, basophiles 3 per cent, lymphocytes 14 per cent, monocytes 6 per cent, hematocrit 44 per cent cells. The blood Wassermann test was negative. The blood non-protein nitrogen was 32 mg. per 100 cc., blood sugar 80 mg. per 100 cc., plasma CO_2 combining power 52.2 volumes per cent, total plasma protein 5.75 gms. per 100 cc., plasma concentration of sodium 134.2 m.eq., of chloride 100.8 m.eq. and of potassium 4.0 m.eq. per liter. The urine and stools were normal. An x-ray of the chest was normal. The basal metabolic rate was plus 5 per cent and an electrocardiographic record was normal. Subsequent observations are recorded in the text.

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BOOK REVIEWS

(The reviews represent the individual opinions of the reviewers and not neceessarily those of the members of the Editorial Board of the Journal.)

Trauma and Disease. Edited by LEOPOLD BRAHDY AND SAMUEL KAHN. 613 pp. Illus. $7.50. (*Lea and Febiger, Philadelphia, 1937.*)

The purpose of this book is to fill a need which has become progressively more pressing in recent years, for a wider and more accurate knowledge of the relations that exist between trauma and disease. Not many years ago, little thought was given to this problem; the physician was interested only in the direct causes of disease, in diagnosis, and in treatment, and looked with indifference on the study of the secondary factors in etiology. At the present time, however, the increasing accident rate, the compensation laws, and the growth of preventive and industrial medicine have made necessary a thorough consideration of this subject.

The authors divide diseases, according to their relation to trauma, into three groups:

1. Those which are practically always the direct result of trauma, such as fractures and lacerations.
2. Those which are never the result of a single trauma. In some diseases, such as measles, this is obvious; in others, such as colloid goiter or Köhler's disease of the metatarsals, the evidence must be carefully evaluated.
3. Those which usually develop without trauma, but in which trauma may be a causative factor, for example, angina pectoris, kidney abscess and exophthalmic goiter.

Authorities have contributed the chapters in their individual fields. Trauma is discussed in its relation to diseases of the heart, peripheral blood vessels, lungs, gastro-intestinal tract and genito-urinary tract; to obstetrics and gynecology; to disorders of the mental apparatus; to syphilis; to diseases of the nervous system, bones, joints and spine; and to conditions such as neoplasms, diabetes, thyroid disease and blood diseases.

Although the organic systems are not covered in regular sequence and although there is a certain overlapping of information, the subjects are clearly and thoroughly presented, and the book is of great value especially from a medico-legal point of view.

I. R. T.

Synopsis of Clinical Laboratory Methods. By W. E. BRAY. 2nd ed. 408 pp. Illus. (*C. V. Mosby Co., St. Louis, 1938.*)

The second edition of this compact little handbook of clinical laboratory

methods has been brought up to date by the addition of a number of recently developed procedures which should prove useful to the practitioner and the clinical pathologist alike. Among these are the determination of cyanates in the blood, the determination of sulfanilamide in the blood, vitamin C titration, the differential heterophile agglutination for infectious mononucleosis, the cough plate method for the diagnosis of whooping cough, and the opsonocytophagic test for determining the immunity status in undulant fever. Since the descriptions of the various methods are necessarily brief in a book of this type, the author wisely includes references to the original articles in a number of instances. The two longest chapters are devoted to hematology and bacteriology.

Certain of the procedures advocated are open to criticism as for example the test for porphyrin in urine. Furthermore the reviewer cannot agree with the author that a leucocyte count and hemoglobin determination *once a week* constitute sufficient blood work in a case of typhoid fever.

The type is of necessity small and the illustrations consist largely of drawings, some of which are colored, although a number of fairly good photomicrographs are included.

On the whole it may be said that the good points far outweigh the faults and the book may be recommended for the purpose which it is designed to fulfill.

W. H. B.

The Etiology of Trachoma. By LOUIS A. JULIANELLE. [Chairman of the Trachoma Commission. Washington University, St. Louis.] 248 pp. Illus. $3.25. (*The Commonwealth Fund, New York, 1938.*)

This is a complete and scholarly review of the literature and various theories on the etiology of trachoma by a distinguished investigator in this field. The first chapter gives a concise, but adequate, account of the symptomatology and differential diagnosis of trachoma. Thereupon follow four chapters giving a general discussion of epidemiology, etiology, infectivity, and various organisms associated with trachoma. The remaining five chapters discuss the virus etiology of trachoma in its various manifestations, and give not only an excellent review of the literature but also a complete summary of the author's extensive researches.

The researches of Julianelle and others have clearly established the fact that trachoma is an infectious disease, that the infectious agent is one of remarkable frailty and low infectivity, frequently not filterable, of weak propagative and poor immunologic properties. It is far from clearly established, however, whether the infectious agent is a virus, an inclusion body or a rickettsia. The author definitely inclines to the view it is a virus but is unwilling to abandon completely the idea that inclusion bodies may be concerned. The extensive literature indicative that the inclusion bodies, both initial and elementary, are detritus or disintegrated bacteria phagocytosed by the epithelial cells is fairly and clearly presented, but is discounted by the author for reasons not completely convincing.

The entire monograph is extremely well written, the diction excellent, and the presentation clear. It gives in concise form not only the results of years of

laboratory investigation, but also an epitome of voluminous, and, alas, garrulous literature on trachoma. The volume should be on the shelves of everyone interested in the experimental investigation of ocular disease.

A. C. W.

Scoliosis: A New Study of an Old Problem. By OSCAR H. ALLIS, M.D., LL.D. 168 pp. Illus. (*Privately printed, Philadelphia, 1938.*)

Although this monograph is published seventeen years after the death of the author, it nevertheless has considerable contemporary interest. Written in a vigorous style and illustrated by appropriate sketches, it presents a thesis that is definitely unique and thought-provoking. The basic concept that is presented is that scoliosis is *not* a primary deformity of the spine. It is due to a distortion of the true ribs which, in turn, twists the spine out of shape. The change in the alignment of the ribs develops as a result of "unsymmetrical, sitting, habit posture," *i.e.*, the posture assumed in the "penman" position.

Undoubtedly this theory was quite unorthodox at the time that it was promulgated. The last decade has given us information which might make the theory less objectionable. The asymmetrical pull of abdominal muscles following infantile paralysis has been known to twist the ribs and through them to produce a scoliosis. Nevertheless, the thesis is too far afield from the standard line of thought to be accepted in the form presented. The presentation of satisfactory case reports would have helped considerably to substantiate the author's position. One cannot help wishing that the essayist had lived and had had opportunity to develop his thesis more completely.

I. W. N.